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WO 03/040077 A1

(54) Title: COMBRETASTATIN A-4 DERIVATIVES HAVING ANTINEOPLASTIC ACTIVITY

(57) Abstract: Compounds are disclosed that are designed to mimic the activity of combretastatin A-4 based on chalcone, aurone, or indanone structures, or involving benzoquinone or quinone rings. The anti-cancer activity of exemplified compounds is demonstrated in a range of in vitro and in vivo assays.

COMBRETASTATIN A-4 DERIVATIVES HAVING ANTINEOPLASTIC ACTIVITY

Field of the Invention

The present invention relates to compounds and their uses, and more particularly to chalcone, indanone, aurone and quinone compounds which are structurally related to combretastatin A-4 and their possible use as anticancer compounds. The present invention also relates to the use of these and other compounds in the treatment of cancer.

Background of the Invention

The stilbene *cis*-combretastatin A-4, isolated from the African bush willow, *Combretum caffrum* shows exciting potential as an anticancer agent, binding strongly to tubulin and displaying potent and selective toxicity toward tumour vasculature (US Patent No:4,996,237. *cis*-combretastatin A-4 is able to inhibit cell growth at low concentrations (IC_{50}, P388 murine leukaemia cell line 2.6 nM). The potency of *trans*-combretastatin A-4 is much lower and inhibits cell growth in the μM range. Arguably, it is the ability of *cis*-combretastatin A-4 to destroy tumour blood vessels, effectively starving tumours of nutrients, which makes them such exciting molecules. Tumour vasculature and the formation of neovasculature were first identified as a target for cancer therapy by Judah Folkman some 30 years ago. The work of Folkman and others has clearly identified angiogenesis and blood supply as necessary requirements for primary tumour growth, invasiveness and metastasis. It is now becoming clear that the selective destruction of tumour vasculature will have a significant impact on the clinical treatment of cancer. Angiogenesis is subject to a complex process of regulation and thereby offers a multitude of molecular targets for drug design.

We have previously investigated the tubulin-binding properties of agents related to CA-4 and colchicine and as part of this effort, we have designed many related compounds that behave in a similar fashion to CA-4 (Ducki et al, *Bioorg. Med. Chem. Lett.*, 1998, 8, 1051; Zhao et al, *Eur. J. Nuc. Medicine*, 1999, *26*, 231; Aleksandrzak et al, *Anti-Cancer Drugs*, 1998, *9*, 545).

Considerable effort has been expended in an attempt to synthesis and characterise compounds suitable for use in anti-tumour therapies. By way of example, US Patent No: 6,071,930 describes the synthesis of a series of 2-aryl-1,8-naphthyridiones, which have amino analogues of cytotoxic antimitotic flavonoids. The authors found that many of these compounds were cytotoxic and possessed activity against tubulin polymerisation and colchicine binding.

EP 0 288 794 A2 describes the use of a number of chalcone derivatives bearing either $-NR_2$ or -NHCOR groups (where R is C_1-C_4 alkyl), for treating growth of tumour tissues.

Clark et al, in the international patent application WO00/35865, disclose natural product derivatives and derivatives of known tubulin-binding compounds in which a (poly)fluorobenzene, fluoropyridine, or fluoronitrophenyl moiety is incorporated or added to the structure. These derivatives can be used as antimitotic agents.

Ring-contracted analogues of the antitumour agent etoposide have been prepared by Klein et al. and the cytotoxicity of the derivatives towards several tumour cell lines has also been reported.

Beutler et al have screened over 70 known flavones for cytotoxicity in the NCI in vitro 60-cell line human tumour screen. The tests demonstrated that flavones which are not substituted at the carbon alpha to the ketone have a minimal cytotoxicity.

Compounds isolated from leaf and stem extracts of *Uvaria hamiltonii* were tested for activity in a 9KB cytotoxicity assay. In contrast to the studies of Beutler et al., flavanones and aurones were found to be inactive, and chalcone compounds demonstrated only weak activity.

Despite ongoing attempts to synthesis compounds with anti-tumour activity, it remains a problem in the art in designing effective compounds.

Summary of the Invention

At its broadest, the present invention provides new potential anti-cancer compounds, structurally related to combretastatin A-4, and their use, along with related compounds, in the treatment of cancer and other conditions involving abnormal proliferation of vasculature.

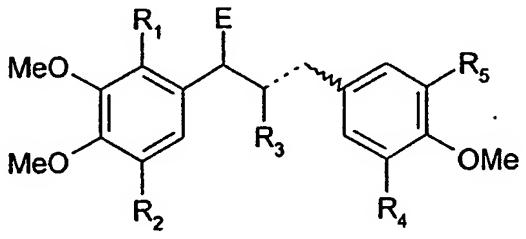
The compounds of the present invention represent a new range of potential anti-tumour drugs.

In some embodiments, the compounds of the present invention are based on the chalcone structure and are either substituted chalcones or conformationally restricted analogues of chalcones, all being related to the CA-4 structure.

The synthesis of new compounds is disclosed herein, together with experiments demonstrating their activity in cytotoxicity (IC_{50}) assays against the K562 cell line and supporting their use as anticancer compounds and prodrugs.

Accordingly, in a first aspect, the present invention provides a family of anti-cancer compounds based on chalcone, indanone, aurone and quinone structures, including fluorinated, nitro, amine and phosphate substituted analogues. The family of compounds includes structures where the ketone has been reduced to an alcohol, alkene or alkane.

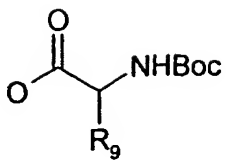
Thus, in this aspect, the present invention provides compounds represented by the structural formula (I):



(I)

wherein:

E represents an oxo (=O) or a hydroxyl (-OH);
the dashed line indicates that a single or double bond may be present;
the zig-zag line indicates that the compound can be either the E or Z isomer;
R_3 is H, alkyl, CH_2NH_2, CH_2NHalkyl, CH_2OH, $CH_2N(alkyl)_2$, $CH_2NH(C=O)$alkyl, $CH_2NH(C=O)$aryl; and
R_4 is H, halogen, NH(alkyl), $N(alkyl)_2$, $NH(C=O)$alkyl, $NH(C=O)$aryl, or a Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain; and further wherein

when E is an oxo (=O) group and the dashed line represents a single bond,
R_1 is H; R_2 is alkoxy; R_4 is H; and R_5 is OH; or

when E is an oxo (=O) group and the dashed line represents a double bond,
R_1 is H; R_2 is alkoxy; R_4 is H or halogen; and
R_5 is H or halogen; or
R_4 is H; and R_5 is NH_2, NO_2, halogen or $OPO_3(R_6)_2$; where R_6 is H, CH_2Ph or a metal cation; or
R_1 is alkoxy; R_2 is H; R_4 is H or halogen; and
R_5 is halogen or OH; or

when E is a hydroxyl (-OH) group and the dashed line represents a single or double bond,
R_1 is H; R_2 is alkoxy; R_3 is methyl; R_4 is H; and R_5 is OH;

or a salt or derivative thereof.

In all aspects of the invention, preferably, the substituents are chosen according to the following list of preferred groups.

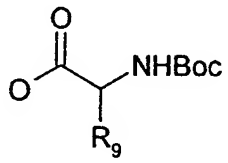
Preferably, alkyl or alkoxy substituents are substituted or unsubstituted, branched or unbranched C_{1-10} alkyl or alkoxy groups. Preferred alkyl substituents are methyl

or ethyl. Preferred alkoxy substituents are methoxy, ethoxy or propoxy.

Halogen substituents can be fluorine, chlorine, bromine or iodine, and are preferably fluorine.

As used herein, preferably R and R' are substituted or unsubstituted, branched or unbranched C_{1-10} alkyl groups or aryl or heteroaryl groups.

As used herein, the Boc-ester group wherein X is a group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain, and Boc represents a t-butoxycarbonyl group. The amino acid ester side chain may include a naturally occurring or synthetic amino acid, in either the D or L-isoform. Examples of compounds of the aspect of the invention include those where the amino acid is Phe, Ile, Gly, Trp, Met, Leu, Ala, His, Pro, D-Met, D-Trp, or Tyr, e.g. when the amino acid is Phe, R_9 group is $-CH_2Ph$ etc. Further information on the preparation of Boc esters is provided in WO 02/50007.

In a preferred embodiment, the present invention provides a compound represented by formula (I) where:

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5

is OH (MW57);

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is OH (MW71);

E is an oxo (=O) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is NH_2 (MW65);

E is an oxo (=O) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is NO_2 (MW47);

E is an oxo (=O) group; the dashed line represents a double bond; the compound is the E isomer; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is NO_2 (MW68);

E is an oxo (=O) group; the dashed line represents a double bond; the compound is the Z isomer; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is NO_2 (MW69);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is F (DR2);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is F; and R_5 is F (DR3);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is F (DR5);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is F; and R_5 is F (DR6);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is OMe; R_2 is H; R_3 is H; R_4 is H; and R_5 is OH (DR8);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is OMe; R_2 is H; R_3 is H; R_4 is H; and R_5 is F (DR9);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is OMe; R_2 is H; R_3 is H; R_4 is F; and R_5 is F (DR10);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is CH_2Ph (DR53);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is CH_2Ph (DR54);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is H (DR55);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is H (DR56);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is H (SD173a);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is Na (SD174a);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is Na (SD174b);

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is OH (MW72);

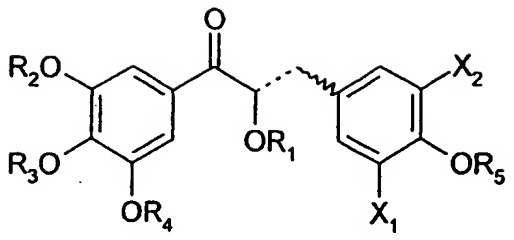
E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is OH (MW58);

E is a hydroxyl (-OH) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is OH (MW50);

E is a hydroxyl (-OH) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is OH (MW70);

In this aspect, the present invention provides a further family of compounds based on the chalcone structure, including fluorinated analogues.

Accordingly, the present invention provides compounds represented by the structural formula (Ia):

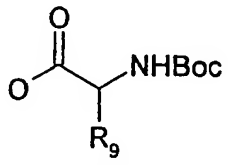


wherein:

the dashed line indicates that a single or double bond may be present;

the zig-zag line indicates that the compound can be either the E or Z isomer;

R_1 is alkyl; R_2, R_3, R_4 and R_5 are independently selected from H or alkyl; X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-P=O(OR)$_2$, O-aryl, O-heteroaryl, O-ester or a Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain;

or a salt or derivative thereof.

In a preferred embodiment, the present invention provides: a compound represented by formula (Ia) when

the dashed line represent a double bond; R_1 is Me; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is OH (DR13); or

the dashed line represent a double bond; R_1 is Me; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is F (DR14); or

the dashed line represent a double bond; R_1 is Me; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 and X_2 are F (DR15); or

the dashed line represent a double bond; R_1 is Et; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is OH (DR16); or

the dashed line represent a double bond; R_1 is Et; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is F (DR17); or

the dashed line represent a double bond; R_1 is Et; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 and X_2 are F (DR18); or

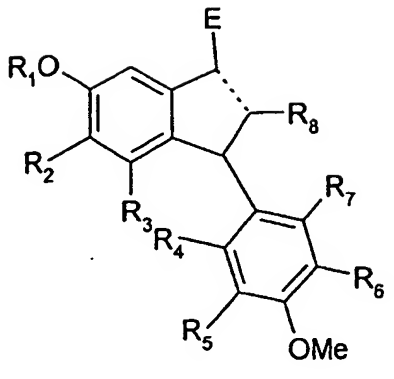
the dashed line represent a double bond; R_1 is Pr; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is OH (DR19); or

the dashed line represent a double bond; R_1 is Pr; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is F (DR20); or

the dashed line represent a double bond; R_1 is Pr; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is F; and X_2 is F (DR21);

In this aspect, the present invention provides a family of compounds based on the indanone structure, including reduced forms of the ketone, and fluorinated analogues.

Accordingly, the present invention provides compounds represented by the structural formula (II):



(II)

wherein:

E represents an oxo (=O), hydroxyl (-OH) or a hydrogen atom;

the dashed line in the structure indicates that a single or double bond may be present; and

R_8 is hydrogen, alkyl, aryl, CH_2NH_2, CH_2NHalkyl or $CH_2N(alkyl)_2$; and wherein

when E is an oxo (=O) group and the dashed line represents a single bond,

R_1 is alkyl or H; R_2 is alkoxy or H; R_3 is alkoxy or H; and R_4 is H; R_5 is H, $O(P=O)(OR)_2$ or Boc-ester; R_6 is NO_2, NH_2, H, OH, halogen, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H; or

R_4 is H; R_5 is halogen, $O(P=O)(OR)_2$ or Boc-ester; R_6 is OH, halogen, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H; or

R_4 is alkoxy; R_5 is H, $O(P=O)(OR)_2$ or Boc-ester; R_6 is H, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is alkoxy; or

when E is a hydroxyl (-OH) group and the dashed line represents a single bond,

R_1 is alkyl; R_2 is H or alkoxy; R_3 is alkoxy; R_4 is H; R_5 is alkoxy, halogen, $O(P=O)(OR)_2$ or Boc-ester;

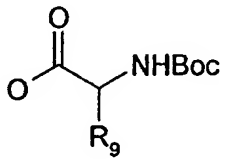
R_6 is H, NO_2, NH_2, OH, halogen, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H; or

when E is a hydrogen atom and the dashed line represents a double bond,

R_1 is Me; R_2 is alkoxy; R_3 is alkoxy; R_4 is H; R_5 is H, $O(P=O)(OR)_2$ or Boc-ester;

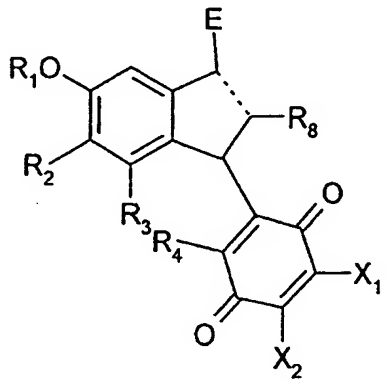
R_6 is NO_2, NH_2, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H;

wherein the Boc-ester is a group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain; or

a compound represented by structural formula (IIa),



(IIa)

wherein:

E, R_1, R_2, R_7 and R_8 are as defined above; and
X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-aryl, O-heteroaryl or O-ester; or

or salts and derivatives of compounds II or IIa.

In a preferred embodiment, the present invention provides: a compound represented by formula (II) when E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; R_7 is H (MW73); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NH_2; and R_7 is H (MW74); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is H; and R_7 is H (DM23); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM13); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is H; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM25); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OH; R_3 is H; R_4 is OMe; R_5 is H; R_6 is H; and R_7 is OMe (DM26); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is F; and R_7 is H (DR59); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is F; R_6 is F; and R_7 is H (DR61); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; R_7 is H (MW76); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NH_2; and R_7 is H (MW77); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is H; and R_7 is H (DM28); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM29); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is H; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM31); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is F; and R_7 is H (DR60); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is F; R_6 is F; and R_7 is H (DR62); or

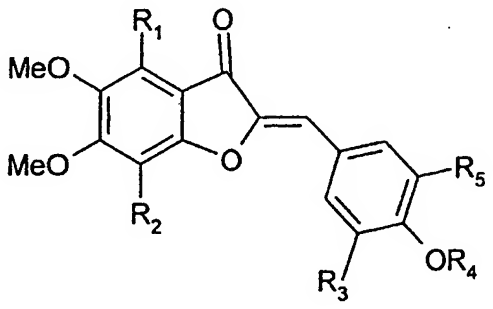
E is a hydrogen atom; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; and R_7 is H (MW75); or

E is a hydrogen atom; the dashed line represents a double bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; and R_7 is H (MW81); or

E is a hydrogen atom; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NH_2; and R_7 is H (MW82); or

In this aspect, the present invention provides a family of compounds based on the aurone structure, including fluorinated analogues.

Accordingly, the present invention provides compounds represented by the structural formula (III):

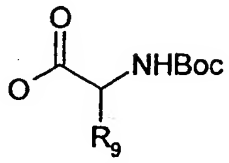


(III)

wherein:

R_1 is H or alkoxy; R_2 is H or alkoxy; R_3 is H or halogen; R_4 is H or alkyl; and R_5 is H, OH, halogen, $O(P=O)(OR)_2$ or

a Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain; or a salt or derivative thereof.

In a preferred embodiment, the present invention provides: a compound represented by formula (III) when

R_1 is OMe; R_2 is H; R_3 is H; R_4 is Me; R_5 is H (DR22); or

R_1 is OMe; R_2 is H; R_3 is H; R_4 is Me; R_5 is OH (DR23); or

R_1 is OMe; R_2 is H; R_3 is H; R_4 is Me; R_5 is F (DR24); or

R_1 is OMe; R_2 is H; R_3 is F; R_4 is Me; R_5 is F (DR25); or

R_1 is H; R_2 is OMe; R_3 is H; R_4 is Me; R_5 is H (DR26); or

R_1 is H; R_2 is OMe; R_3 is H; R_4 is Me; R_5 is OH (DR27); or

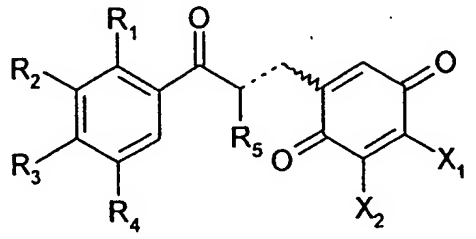
R_1 is H; R_2 is OMe; R_3 is H; R_4 is Me; R_5 is F (DR28); or

R_1 is H; R_2 is OMe; R_3 is F; R_4 is Me; R_5 is F (DR29); or

R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; R_5 is OH (DR31).

In a further aspect, the present invention provides a family of compounds with a substituted or unsubstituted benzoquinone/quinone ring.

Accordingly, the present invention provides compounds represented by the structural formula (IV):



(IV)

wherein:
the dashed line indicates that a single or double bond may be present;
the zig-zag line indicates that the compound can be either the E or Z isomer; and
R_1, R_2, R_3 and R_4 are independently selected from H or alkoxy;
R_5 is hydrogen, alkyl, alkoxy or O-aryl; and
X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-aryl, O-heteroaryl or O-ester;
or a salt or derivative thereof.

In a preferred embodiment, the present invention provides: a compound represented by the formula (IV) when

the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is OMe; R_4 is OMe, X_1 is OMe, and X_2 is H.

In a further aspect, the present invention provides a pharmaceutical composition, comprising one or more compounds as defined above, their salts or a mixture of both.

The use of amine functional groups in the compounds means that they can form salts and by variation of the salts (counterion, etc), the solubility properties of the compound can be altered. Variation of the salt (counterion, etc) represents another method of directing the activity of the compound, and forms part of the present invention.

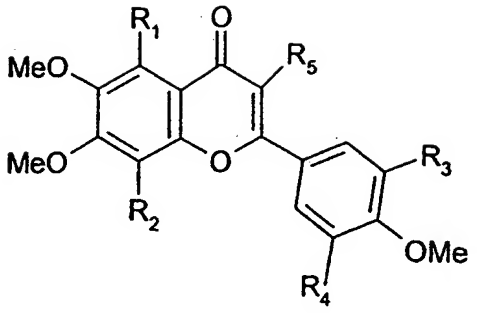
The compounds disclosed here have been prepared and tested as racemic mixtures. It is expected that the pure enantiomers are likely to posses altered activity, one enantiomer being significantly more active than the other. The compounds of the invention will bind to proteins in the course of their action and therefore the chirality of the compound is likely to be important in determining their effectiveness.

Therefore, the individual enantiomers of compounds disclosed herein also form part of the present invention.

In a further aspect, the present invention provides a compound as defined above for use in a method of medical treatment.

In a further aspect, the present invention provides the use of a compound as defined above for the preparation of a medicament for the treatment of cancer or another condition involving abnormal proliferation of vasculature. Examples of these conditions include diabetic retinopathy, psoriasis and endometriosis.

In addition, the present invention provides compounds represented by the structural formulae (V) and (Va) and their use in a method of medical treatment:



(V)

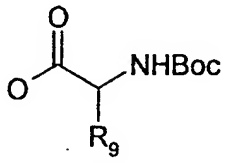
wherein:

R_1 or R_2 is alkoxy and the other is H;

R_3 and R_4 are different and are hydrogen, halogen, OH, $O(P=O)(OR)_2$ or Boc-ester;

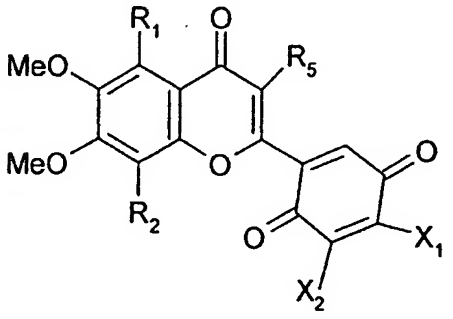
R_5 is aryl, alkyl or O-alkyl;

wherein the Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain; or

a compound of represented by structural formula (Va) in which:



(Va)

wherein:

R_1, R_2 and R_5 are defined as above;

X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-aryl, O-heteroaryl or O-ester; or

or salts and derivatives of compounds V or Va.

In a preferred embodiment, the present invention provides: a compound used in a method of medical treatment, represented by formula (V) when R_1 is OMe; R_2 is H; R_3 is OH; and R_4 is H; or

R_1 is OMe; R_2 is H; R_3 is F; and R_4 is H; or

R_1 is H; R_2 is OMe; R_3 is OH; and R_4 is H; or

R_1 is OMe; R_2 is H; R_3 is F; and R_4 is H.

In a further aspect, the present invention provides the use of a compound as defined above for the preparation of a medicament for the treatment of cancer or another condition involving abnormal proliferation of vasculature. Examples of these conditions include diabetic retinopathy, psoriasis and endometriosis.

Embodiments of the present invention will now be described by way of example and not limitation with reference to the accompanying figures.

Brief Description of the Figures

Figure 1 shows the base catalysed condensation of an aldehyde and acetophenone to form chalcone structures.

Figure 2 shows the Knoevenagel-like condensation of

substituted acetophenone and benzaldehyde.

Figure 3 shows the trifluoroacetic acid catalysed ring closure of chalcones to form indanones.

Figure 4 shows the base catalysed formation of aurones.

Figure 5 shows the results of treating H460 xenograft mice with compound DR5 compared to control.

Figure 6 shows the results of treating H460 xenograft mice with compound DR5 in combination with X-ray treatment compared to control.

Detailed Description

Pharmaceutical Compositions

The compounds of the invention may be derivatised in various ways. As used herein "derivatives" of the compounds includes salts, esters such as *in vivo* hydrolysable esters, free acids or bases, hydrates, prodrugs or coupling partners. In the case of compounds which are combretastatin or analogues thereof, preferably the derivatives are soluble in water and/or saline or can be hydrolysed to provide physiologically active agents.

Examples in the prior art of salts or prodrugs of *cis*-combretastatin A-4 focus on forming salts or derivatives at the phenolic hydroxyl group of combretastatin. These include sodium phosphate salts, sodium and potassium salts (US Patent No: 5,561,122), lithium, caesium, magnesium, calcium, manganese and zinc salts of *cis*-combretastatin A-4, and ammonium cation salts with imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine,

quinidine, tetracycline and verapamil (WO99/35150).

Without wishing to be bound by any particular explanation, the inventors believe that compounds of the invention including quinone and benzoquinone groups are activated in vivo by enzymes such as DT-diaphorase, reducing or hydrolysing the compounds to produce active forms of them. Thus, compounds including the quinone or benzoquinone groups can be regarded as prodrugs for active forms of the compounds, see also WO 02/50007.

Salts of the compounds of the invention are preferably physiologically well tolerated and non toxic. Many examples of salts are known to those skilled in the art. Compounds having acidic groups, can form salts with alkaline or alkaline earth metals such as Na, K, Mg and Ca, and with organic amines such as triethylamine and Tris (2-hydroxyethyl)amine. Salts can be formed between compounds with basic groups, e.g. amines, with inorganic acids such as hydrochloric acid, phosphoric acid or sulfuric acid, or organic acids such as acetic acid, citric acid, benzoic acid, fumaric acid, or tartaric acid. Compounds having both acidic and basic groups can form internal salts.

Esters can be formed between hydroxyl or carboxylic acid groups present in the compound and an appropriate carboxylic acid or alcohol reaction partner, using techniques well known in the art. Examples of esters include those formed between the phenolic hydroxyl of the substituted stilbenes and carboxylic acids, hemisuccinic acid esters, phosphate esters, BOC esters, sulphate esters and selenate esters.

Derivatives which as prodrugs of the compounds are convertible *in vivo* or *in vitro* into one of the parent compounds. Typically, at least one of the biological activities of compound will be reduced in the prodrug form of the compound, and can be activated by conversion of the prodrug to release the compound or a metabolite of it. Examples of prodrugs include phosphate derivatives.

Other derivatives include coupling partners of the compounds in which the compounds is linked to a coupling partner, e.g. by being chemically coupled to the compound or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody or an inhibitor. Coupling partners can be covalently linked to compounds of the invention via an appropriate functional group on the compound such as a hydroxyl group, a carboxyl group or an amino group.

The compounds described herein or their derivatives can be formulated in pharmaceutical compositions, and administered to patients in a variety of forms, in particular to treat conditions which are ameliorated by the activation of the compound.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder, cream, liquid form or encapsulated by liposomes. A tablet may include a solid carrier such as gelatin or an adjuvant or an inert diluent. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, or glycols such as

ethylene glycol, propylene glycol or polyethylene glycol may be included. Such compositions and preparations generally contain at least 0.1wt% of the compound.

Parental administration includes administration by the following routes: intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraocular, transepithelial, intraperitoneal and topical (including dermal, ocular, rectal, nasal, inhalation and aerosol), and rectal systemic routes. For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, solutions of the compounds or a derivative thereof, e.g. in physiological saline, a dispersion prepared with glycerol, liquid polyethylene glycol or oils.

In addition to one or more of the compounds, optionally in combination with other active ingredient, the compositions can comprise one or more of a pharmaceutically acceptable excipient, carrier, buffer, stabiliser, isotonicizing agent, preservative or anti-oxidant or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material may depend on the route of administration, e.g. orally or parentally.

Liquid pharmaceutical compositions are typically formulated to have a pH between about 3.0 and 9.0, more

preferably between about 4.5 and 8.5 and still more preferably between about 5.0 and 8.0. The pH of a composition can be maintained by the use of a buffer such as acetate, citrate, phosphate, succinate, Tris or histidine, typically employed in the range from about 1 mM to 50 mM. The pH of compositions can otherwise be adjusted by using physiologically acceptable acids or bases.

Preservatives are generally included in pharmaceutical compositions to retard microbial growth, extending the shelf life of the compositions and allowing multiple use packaging. Examples of preservatives include phenol, meta-cresol, benzyl alcohol, para-hydroxybenzoic acid and its esters, methyl paraben, propyl paraben, benzalconium chloride and benzethonium chloride. Preservatives are typically employed in the range of about 0.1 to 1.0 % (w/v).

Preferably, the pharmaceutically compositions are given to an individual in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be, although prophylaxis may be considered therapy), this being sufficient to show benefit to the individual. Typically, this will be to cause a therapeutically useful activity providing benefit to the individual. The actual amount of the compounds administered, and rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other

factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980 or Remington's Pharmaceutical Sciences, 19th edition, Mack Publishing Company, Easton, Pa., 1995; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994. By way of example, and the compositions are preferably administered to patients in dosages of between about 0.01 and 100mg of active compound per kg of body weight, and more preferably between about 0.5 and 10mg/kg of body weight .

Experimental

Chalcones were prepared by the base catalysed condensation of an aldehyde and acetophenone. Those bearing a group at the alpha position were prepared by the Knoevenagel-like condensation of the appropriately substituted acetophenone and benzaldehyde.

Compounds disclosed here which have an amine functionality represent an important addition to the range of compounds which demonstrate significant activity. The amine functional groups allow the formation of salts which would enable the solubility properties of the compound to be altered, as well as influence the activity of the compound.

Chalcone structures bearing an alpha-alkoxy group are particularly active compounds.

Fluorinated versions of the chalcone structures are also active. Indeed, compounds with a fluorine at the 3 position on the B-ring demonstrate significant activity and DR5 is the most active fluorinated analogue.

Phosphate derivatives of the present invention also represent potent cytotoxins with enhanced solubility properties. Compounds SD174a and SD174b are potently active.

Indanones were prepared by trifluoroacetic acid catalysed ring closure of chalcones. These provided conformationally restricted chalcone analogues. Indanols were prepared by reduction of the indanones. Further reduction removed the oxygen functionalities altogether and related compounds were synthesised.

The compounds of the invention including quinone rings can be prepared using literature techniques from a monophenol by treatment with Fremy's salt to provide the quinone or from methoxyaryl, hydroxyaryl or aniline starting materials.

The synthesis of Boc-ester derivatives is disclosed in WO 02/50007.

The synthesis of compounds (e.g) of formula I in which the R_4 substituent comprises an amine or amide functional group such as $-CH_2NH-R$, where R is alkyl or $-(C=O)-R$, can be carried out starting from a parent ester. Reaction with BH_3 gives a $-CH_2OH$ group that can be reacted under Mitsunobu conditions to give $-CH_2$-Phthalimide. This can then be alkylated or acylated using standard procedures.

For synthesizing $-CH_2C=O$ compounds, standard techniques can be employed to convert an ester to CH_2OH (as above) then to CH_2Cl then to CH_2CN then to CH_2COOH. The acid can then be transformed into $CH_2(C=O)-NHR$ and $CH_2-(C=O)$-alkyl

or aryl groups.

The most active chalcone structures give the most active indanone compounds. Reduced forms of the indanones are less active than the parent ketone compounds. Interestingly, the highly reduced indanones are more active than the indanols.

Compounds based on the aurone structure were prepared as conformationally restricted analogues of the chalcones. They were prepared from the appropriate benzofuranone. Both DR27 and DR28 have significant activity, with IC_{50} values in the cytotoxicity tests of 50nM and 110nM respectively.

The compounds disclosed here have been prepared and tested as racemic mixtures. It is expected that the pure enantiomers are likely to posses altered activity. The compounds of the invention will bind to proteins in the course of their action and therefore the chirality of the compound is likely to be important in determining their effectiveness.

Synthesis

Representative experimental details are presented here, together with analytical results for the exemplified compounds.

General Methods

Protocol E

To a stirring solution of substituted acetophenone and substituted benzaldehyde in alcohol was added a quantity of an aqueous solution of sodium hydroxide (50% w/v) and the mixture stirred at room temperature under argon

overnight. The mixture was diluted with dichloromethane (50 cm^3) and acidified to pH 1 with an aqueous solution of hydrochloric acid (50 cm^3, 1 N). The separated aqueous layer was extracted further with dichloromethane (2 x 20 cm^3) and the combined organic fractions dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The residue was purified by column chromatography or recrystallisation.

Protocol F

The method adopted was similar to that of Giordano and co-workers (Giordano 1982). To a stirring solution of substituted phenacyl bromide in alcohol was added silver carbonate and boron trifluoride etherate. The solution was stirred at room temperature under argon for 2 days, filtered, diluted with dichloromethane (100 cm^3), washed with water (50 cm^3) and the organic fraction dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography.

Protocol G

The method adopted was that of Varma and co-workers (Varma 1992). To a stirring solution of substituted benzophenone and substituted benzaldehyde in dichloromethane was added neutral alumina and the mixture stirred at room temperature under argon for 1-3 days. The mixture was filtered, diluted with dichloromethane (20 cm^3), washed with distilled water (10 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was purified by either column chromatography or recrystallisation.

Protocol H

The method adopted was that of Wheeler and co-workers (Fitzgerald 1955). A solution of aurone and potassium cyanide in ethanol/dichloromethane was heated at reflux under argon for 12 h. The mixture was poured into water (15 cm^3) and extracted with dichloromethane (3 x 10 cm^3), the combined organic fractions dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography.

3-(3''-Hydroxy-4''-methoxy-phenyl) 3',4',5'-trimethoxy-1-indanone (DM13).

General procedure: A red solution of chalcone (3.05 mmol) in TFA (100 mL) was heated under reflux for 6 hours. The TFA was then distilled and the residue was extracted with chloroform (50-100 mL). The organic extract was treated with $NaHCO_3$ solution (1M, 2 x 50 mL) and water (100 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*, leaving the product as a yellow-brown solid.

The indanone **DM13** was obtained by the general procedure using 1-(3''-hydroxy-4''-methoxyphenyl)-3-(3',4',5'-trimethoxyphenyl)-1-propen-3-one (1 g, 2.9 mmol) in TFA (100 mL), giving a brown solid (910 mg, 91 %).

m.p. 110-112 °C; δ_H (300 MHz, $CDCl_3$) 2.60 (1H, dd, *J* 2.26 Hz, 19.2 Hz, H2a), 3.2 (1H, dd, *J* 7.9 Hz; 19.2 Hz, H2b), 3.45 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.5 (1H, dd, *J* 2.26 Hz, 7.9 Hz, H3), 5.56 (1H, s, OH) 6.6 (1H, d, *J* 1.88 Hz, H2''), 6.65 (1H, dd, *J* 1.88 Hz, 7.91 Hz, H6''), 6.82 (1H, d, *J* 7.91 Hz, H5''), 7.09 (1H, s, H6'); δ_C (75 MHz, $CDCl_3$) 41.4 (CH,

C3), 47.7 (CH2, C2), 56.3, 56.6, 60.5, 61.3 (CH_3), 100.7 (CH, C6'), 111.0 (CH, C2''), 113.7 (CH, C6''), 119.1 (CH, C5''), 132.6, 138.1, 145.0, 145.6, 146.1, 149.2, 150.8, 155.2, 205.8 (C); ν_{max} (KBr disc) 3230 (OH), 1700 (C=O), 1600 (C=C), 1510, 1470, 1350, 1275, 1220 (C-O), 1140, 1100, 1030 cm^{-1}; *m/z* (FAB) 345 [$(M+H)^+$, 100 %]; (Found: C, 66.4; H, 6.0. $C_{19}H_{20}O_6$ requires C, 66.2; H, 5.8 %).

(E)-3-(4"-Methoxy-3"-nitrophenyl)-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (MW47).

A mixture of 3,4,5-trimethoxyacetophenone (2.0 g, 9.5 mmol), 4-methoxy-3-nitrobenzaldehyde(1.7 g, 9.5 mmol) and sodium hydroxide solution (0.4 g in 1 cm^3 of water) in methanol (10 cm^3) was stirred at room temperature overnight. The subsequent mixture was acidified with 1N hydrochloric acid (20 cm^3) and extracted with chloroform (50 cm^3). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallisation from ethyl acetate afforded the chalcone **MW47** as a pale orange solid (2.2 g, 61%).

m.p. 143-145 °C; δ_H (300 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 3.97 (6H, s, OCH_3), 4.02 (3H, s, OCH_3), 7.14 (1H, d, *J* 8.7 Hz, H-5"), 7.29 (2H, s, H-2', H-6'), 7.45 (1H, d, *J* 15.5 Hz, H-2), 7.75 (1H, d, *J* 15.5 Hz, H-3), 7.79 (1H, dd, *J* 8.7 and 2.3 Hz, H-6"), 8.17 (1H, d, *J* 2.3 Hz, H-2"); δ_C (75 MHz, $CDCl_3$) 56.8 (OCH_3), 57.2 (OCH_3), 61.4 (OCH_3), 106.5 (CH), 114.2 (CH), 122.3 (CH), 125.1 (CH), 128.0 (C), 133.5 (C), 134.9 (CH), 140.3 (C), 142.0 (CH), 143.2 (C), 153.6 (C), 154.5 (C), 188.8 (C=O); $\nu_{max.}$ (KBr) 1005 (s), 1030 (w), 1070 (w), 1090 (w), 1130 (s), 1160 (m), 1180 (w), 1215 (m), 1235-1250 (v), 1280 (s), 1310 (w), 1320 (w), 1350 (s), 1420 (s), 1460-1475 (v), 1505 (s),

1530 (s), 1565-1580 (v), 1600 (s), 1620 (m), 1655 (s), 2840 (m), 2930 (w), 2960 (m), 3000 (m), 3040-3070 (v) cm^{-1}; *m/z* (FAB) 374 ($[M+H]^+$, 100%). Found C, 61.3; H, 5.1; N, 3.9%. $C_{19}H_{19}NO_7$ requires C, 61.1; H, 5.1; N, 3.8%.

(E)-3-(3"-Amino-4"-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (MW65).

A mixture of (*E*)-3-(4"-methoxy-3"-nitrophenyl)-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (**MW47**)(1.00 g, 2.7 mmol), tin(II) chloride dihydrate (3.02 g, 13.4 mmol) and concentrated hydrochloric acid (10 drops) in 1:1 ethanol:ethyl acetate (20 cm^3) was stirred and heated to reflux for 2 days. The cooled mixture was diluted with ethyl acetate (30 cm^3) and washed with saturated sodium hydrogen carbonate solution (20 cm^3) followed by brine (20 cm^3). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, chloroform:ethyl acetate 4:1) afforded the chalcone **MW65** as an orange yellow solid (0.29 g, 32%).

m.p. 90-91 °C; R_f 0.49 (SiO_2, chloroform:ethyl acetate 4:1); δ_H (300 MHz, $CDCl_3$) 3.92 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.96 (6H, s, OCH_3), 6.82 (1H, d, *J* 7.9 Hz, H-5"), 7.04 (1H, s, H-2"), 7.07 (1H, d, *J* 7.9 Hz, H-6"), 7.28 (2H, s, H-2', H-6'), 7.31 (1H, d, *J* 15.5 Hz, H-2), 7.73 (1H, d, *J* 15.5 Hz, H-3); δ_C (75 MHz, $CDCl_3$) 56.0 (OCH_3), 56.8 (OCH_3), 61.4 (OCH_3), 106.4 (CH), 110.6 (CH), 113.7 (CH), 119.7 (CH), 121.4 (CH), 128.4 (C), 134.4 (C), 136.9 (C), 142.6 (C), 145.7 (CH), 150.1 (C) 153.5 (C), 189.9 (C=O); $\nu_{max.}$ (KBr) 1000 (m), 1030 (m), 1070 (w), 1130 (s), 1160 (s), 1090 (w0, 1230-1240 (v), 1270 (m), 1300 (w0, 1315 (m), 1335-1355 (v), 1420 (s), 1435-1470 (v), 1510-1520 (v), 1560-1580 (v), 1655 (s), 2840 (m), 2900-2980

(v), 3000 (w), 3370 (s), 3460 (m) cm^{-1}; *m/z* (EI) 343 ($[M]^{+\cdot}$, 100%). Found C, 66.5; H, 6.2; N, 4.1%. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%.

4,5,6-Trimethoxy-3-(4'-methoxy-3'-nitrophenyl)-1-indanone (MW73).

A red solution of (*E*)-3-(4"-methoxy-3"-nitrophenyl)-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (**MW47**)(1.00 g, 2.68 mmol) in TFA (1.7 cm^3) was stirred and heated to reflux overnight. To the cooled solution was added the ice-cold water (20 cm^3). The mixture was extracted with ethyl acetate (50 cm^3). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, hexane:ethyl acetate 2:1) and recrystallisation from 2:1 hexane:ethyl acetate afforded the indanone **MW73** a pale yellow solid (0.76 g, 76%).

m.p. 134-136 °C; R_f 0.21 (SiO_2, hexane:ethyl acetate 2:1); δ_H (300 MHz, $CDCl_3$) 2.57 (1H, dd, *J* 19.2 and 2.6 Hz, H-2), 3.23 (1H, dd, *J* 19.2 and 8.3 Hz, H-2), 3.52 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.60 (1H, dd, *J* 8.3 and 2.6 Hz, H-3), 7.02 (1H, d, *J* 8.7 Hz, H-5'), 7.10 (1H, s, H-7), 7.27 (1H, dd, *J* 8.7 and 2.3 Hz, H-6'), 7.65 (1H, d, *J* 2.3 Hz, H-2'); δ_C (75 MHz, $CDCl_3$) 40.7 (CH), 47.1 (CH_2), 56.7 (OCH_3), 57.0 (OCH_3), 60.6 (OCH_3), 61.3 (OCH_3), 100.8 (CH), 114.2 (CH), 124.8 (CH), 132.5 (C), 133.0 (CH), 137.1 (C), 139.9 (C), 143.2 (C), 149.0 (C), 150.6 (C), 152.0 (C), 155.8 (C), 204.5 (C=O); $\nu_{max.}$ (KBr) 1010 (m), 1030 (w), 1040 (w), 1100 (s), 1135 (s), 1160 (w), 1200 (m), 1215 (m), 1230 (w), 1260 (m), 1280 (s), 1320 (m), 1330 (m), 1350 (s), 1425 (m), 1450-1485 (v), 1520-1540 (b), 1570 (m), 1600 (m),

1625 (m), 1700-1720 (b), 2370 (w), 2840 (w), 2900-2970 (v), 3000 (w) cm^{-1}; *m/z* (FAB) 374 ($[M]^{+\cdot}$, 40%), 43 (100%). Found C, 61.1; H, 5.3; N, 3.7%. $C_{19}H_{19}NO_7$ requires C, 61.1; H, 5.1; N, 3.8%.

3-(3'-Amino-4'-methoxyphenyl)-4,5,6-trimethoxy-1-indanone (MW74).

To a stirring activated suspension of 10% Pd/C (1 spatula) in methanol (5 cm^3) was injected a solution of 4,5,6-trimethoxy-3-(4'-methoxy-3'-nitrophenyl)-1-indanone (**MW73**) (0.20 g, 0.54 mmol) in methanol (20 cm^3). The mixture was stirred at room temperature under a hydrogen atmosphere for 90 min., filtered through celite and evaporated *in vacuo* to give the indanone **MW74** as an orange liquid (0.18 g, 97%).

δ_H (300 MHz, $CDCl_3$) 2.60 (1H, dd, *J* 19.2 and 2.6 Hz, H-2), 3.15 (1H, dd, *J* 19.2 and 7.9 Hz, H-2) 3.42 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.47 (1H, dd, *J* 7.9 and 2.6 Hz, H-3), 6.42 (1H, d, *J* 2.3 Hz, H-2'), 6.50 (1H, dd, *J* 8.3 and 2.3 Hz, H-6'), 6.70 (1H, d, *J* 7.9 Hz, HH-5'), 7.09 (1H, s, H-7); δ_C (75 MHz, $CDCl_3$) 41.5 (CH), 47.8 (CH_2), 55.9 (OCH_3), 56.6 (OCH_3), 60.6 (OCH3), 61.2 (OCH_3), 100.6 (CH), 110.7 (CH), 114.0 (CH), 117.6 (CH), 132.5 (C), 136.6 (C), 137.5 (C), 145.4 (C), 146.5 (C), 149.2 (C), 150.8 (C), 155.1 (C), 206.1 (C=O); $\nu_{max.}$ (KBr) 1005 (w), 1030 (s), 1100 (s), 1130 (s), 1170 (m), 1210-1240 (v), 1260 (w), 1315 (s), 1345 (s), 1420-1430 (v), 1450-1470 (v), 1520 (s), 1600 (s), 1620 (m), 1700-1720 (b), 2840 (m), 2910-2980 (v), 3000 (w), 3380 (s), 3440-3480 (b) cm^{-1}; *m/z* (FAB) 343 ($[M]^{+\cdot}$, 100%). Found C, 66.2; H, 6.1; N, 3.8%. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%.

(E)-3-(3''-Hydroxy-4''-methoxyphenyl)-1-(2',3',4'-trimethoxyphenyl)-2-propen-1-one (DR8).

The chalcone **DR8** was obtained following the general **protocol E** using 2,3,4-trimethoxyacetophenone (0.50 g, 2.38 mmol), 3-hydroxy-4-methoxybenzaldehyde (0.36 g, 2.38 mmol) and sodium hydroxide (0.5 cm^3, 50% w/v) in methanol (10 cm^3), with recrystallisation from methanol affording **DR8** as a yellow solid (0.38 g, 1.56 mmol, 66%).

m.p. 85-86 °C; δ_H (300 MHz, $CDCl_3$) 3.90 (12H, s, OMe), 5.73 (1H, s, OH), 6.74 (1H, d, *J* 8.8 Hz, H-5'), 6.86 (1H, d, *J* 8.1 Hz, H-5''), 7.10 (1H, dd, *J* 8.1 and 2.1 Hz, H-6''), 7.26 (1H, d, *J* 2.1 Hz, H-2''), 7.36 (1H, d, *J* 15.8 Hz, H-2), 7.38 (1H, d, *J* 8.8 Hz, H-6'), 8.61 (1H, d, *J* 15.8 Hz, H-3); δ_C (75 MHz, $CDCl_3$) 56.4 (CH_3), 56.5 (CH_3), 61.4 (CH_3), 62.4 (CH_3), 107.7 (CH), 111.0 (CH), 113.5 (CH), 122.8 (CH), 125.3 (CH), 126.1 (CH), 127.4 (C), 129.2 (C), 142.6 (C), 143.5 (CH), 146.3 (C), 149.0 (C), 154.1 (C), 157.3 (C), 191.3 (C); ν_{max} (KBr disc) 3400, 1600, 1510, 1460, 1270, 1100 cm^{-1}; *m/z* (FAB) 244 [M^+, 65%]; (Found C, 66.2; H, 6.2. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.9%).

(Z)-3-(3''-Hydroxy-4''-methoxyphenyl)-2-methoxy-1-(3',4',5'-timethoxyphenyl)-2-propen-1-one (DR13).

To a stirring solution of 2-methoxy-1-(3',4',5'-trimethoxyphenyl)ethan-1-one (1.00 g, 4.2 mmol) and 3-hydroxy-4-methoxybenzaldehyde (0.64 g, 4.2 mmol) in methanol (15 cm^3) was added sodium hydroxide (6.00 g, 150.0 mmol) to give a solution concentration of 10 N. The mixture was stirred at room temperature under argon

overnight, diluted with water (50 cm^3), acidified to pH 1 with concentrated hydrochloric and extracted with chloroform (2 x 25 cm^3). The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. Purification by column chromatography (SiO_2, hexane:ethyl acetate 2:1) afforded **DR13** as a yellow solid (0.48 g, 1.28 mmol, 31%).

m.p. 120-122 °C; δ_H (300 MHz, $CDCl_3$) 3.77 (3H, s, OMe), 3.91 (6H, s, OMe), 3.93 (3H, s, OMe), 3.94 (3H, s, OMe), 5.62 (1H, s, OH), 6.85 (1H, d, *J* 8.6 Hz, H-5''), 6.46 (1H, s, H-3), 7.18 (2H, s, H-2', H-6'), 7.21 (1H, dd, *J* 8.6 and 2.1 Hz, H-6''), 7.53 (1H, d, *J* 2.1 Hz, H-2''); δ_C (75 MHz, $CDCl_3$) 56.3 (CH_3), 56.7 (CH_3), 58.9 (CH_3), 61.3 (CH_3), 107.5 (CH), 110.8 (CH), 116.3 (CH), 123.7 (CH), 124.6 (CH), 127.8 (C), 133.2 (C), 142.6 (C), 145.8 (C), 147.7 (C), 152.5 (C), 153.4 (C), 192.0 (C); ν_{max} (KBr disc) 3420, 2950, 1650, 1620, 1590, 1500, 1420, 1340, 1130 cm^{-1}; *m/z* (FAB) 374 [M^+, 100%], 195 (100); (Found C, 64.5; H, 6.2. $C_{20}H_{22}O_7$ requires C, 64.2; H, 5.9%).

2-Methoxy-1-(3,4,5-trimethoxy-phenyl-ethanone.

The ketone was obtained following protocol F using *2-bromo-1-(3',4',5'-trimethoxyphenyl)ethan-1-one* (4.18 g, 14.5 mmol), silver(I) carbonate (5.00 g, 18.2 mmol) and boron trifluoride etherate (2.10 cm^3, 16.7 mmol) in methanol (40 cm^3). Purification by column chromatograghy (SiO_2, hexane:ethyl acetate 2:1) afforded the ketone as a white solid (2.57 g, 10.7 mmol, 74%).

m.p. 54-55 °C (Pratt et al 1925 reported m.p. 54 °C); δ_H (300 MHz, $CDCl_3$) 3.51 (3H, s, OMe), 3.93 (9H, s, OMe), 4.68 (2H, s, CH_2), 7.20 (2H, s, H-2', H-6'); δ_C 56.4

(CH_3), 59.5 (CH_3), 61.0 (CH_3), 72.3 (CH_2), 102.0 (CH), 130.1 (C), 143.0 (C), 153.2 (C), 195.0 (C); ν_{max} (KBr disc) 3010, 2950, 1690, 1590, 1420, 1340, 1140 cm^{-1}; *m/z* (FAB) 241 [MH^+, 100%], 195 (90); Found C, 60.1; H, 6.8. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%).

2-Bromo-1-(3',4',5'-trimethoxyphenyl)ethan-1-one.
To a stirring solution of 3,4,5-trimethoxyacetophenone (10.00 g, 47.6 mmol) in dry diethyl ether (450 cm^3) at 0 °C under argon was added bromine (2.70 cm^3, 52.3 mmol) in dry ether (250 cm^3). On completion of addition the flask was irradiated with a 125 W light source for 1 h. The mixture was washed with an aqueous solution (saturated) of sodium metabisulfite (2 x 200 cm^3) and the organic fraction dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. Recrystallisation from diethyl ether afforded *2-bromo-1-(3',4',5'-trimethoxyphenyl)ethan-1-one* as a white solid (11.60 g, 40.3 mmol, 85%).

m.p. 64-66 °C (Horton et al. 1954 reported m.p. 63-67 °C); δ_H (300MHz, $CDCl_3$) 3.94 (9H, s, OMe), 4.41 (2H, s, CH_2), 7.22 (2H, s, H-2', H-6'); δ_C (75 MHz, $CDCl_3$) 30.6 (CH_2), 56.4 (CH_3), 61.1 (CH_3), 106.6 (CH), 129.0 (C), 143.4 (C), 153.2 (C), 190.3 (C); ν_{max} (KBr disc) 2950, 2850, 1690, 1590, 1410, 1340, 1130 cm^{-1}; *m/z* (FAB) 291 [MH^+, ^{81}Br, 40%], 289 [MH^+, ^{79}Br, 45%], 195 (100); Found C, 46.0; H, 4.5. $C_{11}H_{13}O_4Br$ requires C, 45.7; H, 4.5%).

(Z)-3-(3''-Fluoro-4''-methoxyphenyl)-2-methoxy-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (DR14).
The chalcone **DR14** was obtained following protocol E using 2-methoxy-1-(3,4,5-trimethoxyphenyl)-ethanone (0.30 g,

1.25 mmol), 3-fluoro-4-methoxybenzaldehyde (0.19 g, 1.25 mmol) and sodium hydroxide (0.50 cm^3, 3 N) in methanol (4 cm^3), with purification by column chromatography (SiO_2, hexane:ethyl acetate 2:1) affording **DR14** as a yellow solid (0.29 g, 0.77 mmol, 62%).

m.p. 110-112 °C; δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (6H, s, OMe), 3.95 (3H, s, OMe), 6.41 (1H, s, H-3), 6.95 (1H, t, *J* 8.6 Hz, H-5''), 7.19 (2H, s, H-2', H-6'), 7.37 (1H, d, *J* 8.6 Hz, H-6''), 7.74 (1H, dd, *J* 13.0 and 2.0 Hz, H-2''); δ_C (100 MHz, $CDCl_3$) 56.6 (CH_3), 56.8 (CH_3), 59.0 (CH_3), 61.4 (CH_3), 107.4 (CH), 113.2 (CH, d, *J* 3.0 Hz), 117.6 (CH, d, *J* 15.0 Hz), 122.8 (CH, d, *J* 3.0 Hz), 127.3 (CH, d, *J* 6.0 Hz), 127.5 (C, d, *J* 6.0 Hz), 132.9 (C), 142.7 (C), 148.6 (C, d, *J* 15.0 Hz), 152.4 (C, d, *J* 245.0 Hz), 152.9 (C), 153.4 (C), 191.7 (C); δ_F (200 MHz, $CDCl_3$); ν_{max} (KBr disc) 1660, 1610, 1580, 1510, 1470, 1420, 1330, 1270, 1140 cm^{-1}; *m/z* (FAB) 377 [MH^+, 100%]; (Found C, 63.8; H, 5.8. $C_{20}H_{21}O_6F$ requires C, 63.8; H, 5.6%).

(Z)-3-(3'',5''-Difluoro-4''-methoxyphenyl)-2-methoxy-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (DR16).
The chalcone **DR16** was obtained following protocol E using 2-methoxy-1-(3,4,5-trimethoxyphenyl)-ethanone (0.30 g, 1.25 mmol), 3,5-difluoro-4-methoxybenzaldehyde (0.22 g, 1.25 mmol) and sodium hydroxide (0.50 cm^3, 3 N) in methanol (4 cm^3), with purification by column chromatography (SiO_2, hexane:ethyl acetate 3:1) affording **DR16** as a yellow solid (0.37 g, 0.94 mmol, 75%).

m.p. 124-126 °C; δ_H (400 MHz, $CDCl_3$) 3.79 (3H, s, OMe), 3.92 (6H, s, OMe), 3.96 (3H, s, OMe), 4.04 (3H, s, OMe),

6.23 (1H, s, H-3), 7.20 (2H, s, H-2′, H-6′), 7.34 (2H, d, *J* 9.9 Hz, H-2′′, H-6′′); δ_C (100 MHz, $CDCl_3$) 56.8 (CH_3), 59.0 (CH_3), 61.4 (CH_3), 62.3 (CH_3), 107.4 (CH), 114.0 (CH, dd, *J* 13.0 and 3.0 Hz), 119.8 (CH, t, *J* 3.0 Hz), 129.0 (C, t, *J* 7.0 Hz), 132.3 (C), 136.9 (C, t, *J* 13.0 Hz), 143.1 (C), 153.4 (C), 154.1 (C), 155.6 (C, dd, *J* 244.0 and 7.0 Hz), 191.3 (C); δ_F (200 MHz, $CDCl_3$); ν_{max} (KBr disc) 1640, 1580, 1500, 1450, 1330, 1240, 1130 cm^{-1}; *m/z* (FAB) 395 [MH^+, 100%]; (Found C, 61.2; H, 5.4. $C_{20}H_{20}O_6F_2$ requires C, 60.9; H, 5.1%).

(Z)-3-(3′′-Fluoro-4′′-methoxyphenyl)-2-ethoxy-1-(3′,4′,5′-trimethoxyphenyl)-2-propen-1-one (DR17).

The chalcone **DR17** was obtained following protocol E using *2-ethoxy-1-(3′,4′,5′-trimethoxyphenyl)-1-ethanone* (0.30 g, 1.18 mmol), 3-fluoro-4-methoxybenzaldehyde (0.18 g, 1.18 mmol) and sodium hydroxide (1.00 cm^3, 3 N) in ethanol (4 cm^3), with purification by column chromatography (SiO_2, hexane:ethyl acetate 5:2) affording **DR17** as a yellow solid (0.25 g, 0.64 mmol, 54%).

m.p. 89-90 °C; δ_H (300 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.0 Hz, H-5), 3.92 (6H, s, OMe), 3.93 (3H, s, OMe), 3.95 (3H, s, OMe), 3.99 (2H, q, *J* 7.0 Hz, H-4), 6.43 (1H, s, H-3), 6.95 (1H, t, *J* 8.8 Hz, H-5′′), 7.22 (2H, s, H-2′, H-6′), 7.40 (1H, d, *J* 8.8 Hz, H-6′′), 7.80 (1H, dd, *J* 13.2 and 2.2 Hz, H-2′′); δ_C (75 MHz, $CDCl_3$) 16.0 (CH_3), 56.6 (CH_3), 56.7 (CH_3), 61.4 (CH_3), 67.4 (CH_2), 107.4 (CH), 113.3 (CH, d, *J* 3.0 Hz), 117.6 (CH, d, *J* 15.0 Hz), 122.6 (CH, d, *J* 3.0 Hz), 127.2 (CH, d, *J* 6.0 Hz), 127.7 (C, d, *J* 6.0 Hz), 132.7 (C), 142.8 (C), 148.5 (C, d, *J* 15.0 Hz), 152.1 (C), 152.4 (C, d, *J* 245.0 Hz), 153.3 (C), 191.9 (C); δ_F (200 MHz, $CDCl_3$); ν_{max} (KBr disc) 1580, 1520, 1460, 1420, 1330,

1280, 1130 cm^{-1}; *m/z* (FAB) 391 [MH^+, 90%]; (Found C, 64.8; H, 5.7. $C_{21}H_{23}O_6F$ requires C, 64.6; H, 5.9%).

2-Ethoxy-1-(3′,4′,5′-trimethoxyphenyl)-1-ethanone.
The ketone was obtained following protocol F using 2-bromo-1-(3′,4′,5′-trimethoxyphenyl)-1-ethanone (3.00 g, 10.4 mmol), silver(I) carbonate (3.58 g, 13.0 mmol) and boron trifluoride etherate (1.50 cm^3, 12.0 mmol) in ethanol (60 cm^3). Purification by column chromatography (SiO_2, hexane:ethyl acetate 3:1) afforded the ketone as a pale yellow oil (2.42 g, 9.5 mmol, 91%).

δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0 Hz, H-4), 3.63 (2H, q, *J* 7.0 Hz, H-3), 3.90 (9H, s, OMe), 4.68 (2H, s, CH_2), 7.22 (2H, s, H-2′, H-6′); δ_C (100 MHz, $CDCl_3$) 15.5 (CH_3), 56.7 (CH_3), 61.3 (CH_3), 67.6 (CH_2), 74.1 (CH_2), 105.9 (CH), 130.5 (C), 143.3 (C), 153.5 (C), 195.8 (C); ν_{max} (KBr disc) 1700, 1590, 1510, 1460, 1420, 1330, 1240, 1130 cm^{-1}; *m/z* (FAB) 255 [MH^+, 100%].

(Z)-3-(3′′-Fluoro-4′′-methoxyphenyl)-2-propoxy-1-(3′,4′,5′-trimethoxyphenyl)-2-propen-1-one (DR20).
The chalcone **DR20** was obtained following protocol E using 2-propoxy-1-(3′,4′,5′-trimethoxyphenyl)-1-ethanone (0.32 g, 1.19 mmol), 3-fluoro-4-methoxybenzaldehyde (0.18 g, 1.19 mmol) and sodium hydroxide (1.00 cm^3, 3 N) in propanol (4 cm^3), with purification by column chromatography (SiO_2, hexane:ethyl acetate 2:1) affording **DR20** as a yellow solid (0.29 g, 0.72 mmol, 61%).

m.p. 82-83 °C; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.2 Hz, H-6), 1.77 (2H, sextet, *J* 7.2 Hz, H-5), 3.87 (2H, t, *J* 7.2 Hz, H-4), 3.92 (6H, s, OMe), 3.93 (3H, s, OMe), 3.95

(3H, s, OMe), 6.38 (1H, s, H-3), 6.95 (1H, t, *J* 8.5 Hz, H-5''), 7.23 (2H, s, H-2', H-6'), 7.39 (1H, d, *J* 8.5 Hz, H-6''), 7.79 (1H, dd, *J* 13.2 and 2.3 Hz, H-2''); δ_C (100 MHz, $CDCl_3$) 10.8 (CH_3), 23.8 (CH_2), 56.6 (CH_3), 56.7 (CH_3), 61.4 (CH_3), 73.3 (CH_2), 107.7 (CH), 113.3 (CH, d, *J* 3.0 Hz), 117.6 (CH, d, *J* 15.0 Hz), 121.9 (CH, d, *J* 3.0 Hz), 127.2 (CH, d, *J* 6.0 Hz), 127.8 (C, d, *J* 6.0 Hz), 132.7 (C), 142.8 (C), 148.4 (C, d, *J* 15.0 Hz), 152.3 (C, d, *J* 245.0 Hz), 152.4 (C), 153.3 (C), 191.9 (C); δ_F (200 MHz, $CDCl_3$); ν_{max} (KBr disc) 1650, 1580, 1520, 1420, 1240, 1130 cm^{-1}; *m/z* (FAB) 405 [MH^+, 60%]; (Found C, 65.6; H, 6.0. $C_{22}H_{25}O_6F$ requires C, 65.3; H, 6.2%).

2-Propoxy-1-(3',4',5'-trimethoxyphenyl)-1-ethanone.
The ketone was obtained following protocol F using 2-bromo-1-(3',4',5'-trimethoxyphenyl)-1-ethanone (4.00 g, 13.8 mmol), silver(I) carbonate (4.76 g, 17.3 mmol) and boron trifluoride etherate (2.00 cm^3, 15.9 mmol) in propanol (60 cm^3). Purification by column chromatography (SiO_2, hexane:ethyl acetate 2:1) afforded the ketone as a colourless oil (2.30 g, 8.6 mmol, 62%).

δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.2 Hz, H-5), 1.68 (2H, sextet, *J* 7.2 Hz, H-4), 3.53 (2H, t, *J* 7.2 Hz, H-3), 3.91 (9H, s, OMe), 4.68 (2H, s, CH_2), 7.25 (2H, s, H-2', H-6'); δ_C (100 MHz, $CDCl_3$) 10.9 (CH_3), 23.3 (CH_2), 56.7 (CH_3), 61.4 (CH_3), 73.9 (CH_2), 74.4 (CH_2), 106.0 (CH), 130.6 (C), 143.3 (C), 153.5 (C), 196.0 (C); ν_{max} (KBr disc) 1700, 1590, 1500, 1460, 1420, 1240, 1130 cm^{-1}; *m/z* (FAB) 269 [MH^+, 70%]; (Found C, 62.9; H, 7.3. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%).

2-[(Z)-(3'-Hydroxy-4'-methoxyphenyl)methylidene]-5,6,7-trimethoxy-1-benzofuran-3-one (DR27).

The aurone **DR27** was obtained following protocol G using *5,6,7-trimethoxy-1-benzofuran-3(2H)-one* (0.21 g, 0.94 mmol), 3-hydroxy-4-methoxybenzaldehyde (0.14 g, 0.94 mmol) and neutral alumina (3.00 g) in dichloromethane (2 cm^3) stirring for 3 days, with purification by column chromatography (SiO_2, hexane:ethyl acetate 1:1) affording **DR27** as an orange solid (0.16 g, 0.45 mmol, 48%).

m.p. 192-193 °C; δ_H (300 MHz, $CDCl_3$) 3.89 (3H, s, OMe), 3.97 (3H, s, OMe), 4.04 (3H, s, OMe), 4.23 (3H, s, OMe), 5.70 (1H, s, OH), 6.82 (1H, s, H-8), 6.94 (1H, d, *J* 8.4 Hz, H-5'), 7.00 (1H, s, H-4), 7.39 (1H, dd, *J* 8.4 and 1.9 Hz, H-6'), 7.59 (1H, d, *J* 1.9 Hz, H-2'); δ_C (75 MHz, $CDCl_3$) 56.4 (CH_3), 56.8 (CH_3), 61.6 (CH_3), 62.0 (CH_3), 99.7 (CH), 111.1 (CH), 113.6 (CH), 117.2 (CH), 125.4 (CH), 126.2 (C), 139.3 (C), 146.2 (C), 146.7 (C), 148.6 (C), 149.3 (C), 150.9 (C), 154.2 (C), 184.1 (C); ν_{max} (KBr disc) 3250, 1690, 1640, 1590, 1500, 1350, 1290 cm^{-1}; *m/z* (FAB) 359 [MH^+, 100%]; (Found C, 64.1; H, 5.0. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.1%).

5,6,7-Trimethoxy-1-benzofuran-3(2H)-one.

The method adopted was that of Mahajan and co-workers (Mahajan 1996). A solution of 2,3,4-trimethoxyphenoxyacetic acid (3.87 g, 16.0 mmol) in polyphosphoric acid (75 cm^3) was heated at 80 °C under argon for 8 h. The mixture was poured into water (250 cm^3) and extracted with dichloromethane (4 x 50 cm^3), and the combined organic fractions dried over anhydrous magnesium sulfate and evaporated *in vacuo*. Purification by column chromatography (SiO_2, hexane:ethyl acetate 2:1)

afforded *5,6,7-trimethoxy-1-benzofuran-3(2H)-one* as a pale brown solid (2.08 g, 9.3 mmol, 58%).

m.p. 81-83 °C; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OMe), 3.99 (3H, s, OMe), 4.02 (3H, s, OMe), 4.62 (2H, s, CH_2), 6.82 (2H, s, H-2, H-6); δ_C (100 MHz, $CDCl_3$) 56.7 (CH_3), 61.5 (CH_3), 61.8 (CH_3), 75.5 (CH_2), 98.6 (CH), 116.2 (C), 139.5 (C), 150.0 (C), 150.5 (C), 163.3 (C), 199.2 (C); ν_{max} (KBr disc) 1690, 1610, 1480, 1260, 1110 cm^{-1}; *m/z* (FAB) 225 [MH^+, 80%]; (Found C, 59.0; H, 5.4. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%).

2,3,4-Trimethoxyphenoxyacetic acid.

The method adopted was similar to that of Abraham and co-workers (Abraham 1984). To a solution of 2,3,4-trimethoxyphenol (6.60 g, 35.9 mmol) in anhydrous dimethylformamide (100 cm^3) was added sodium hydride (2.16 g, 89.8 mmol) and chloroacetic acid (3.39 g, 35.9 mmol) in anhydrous dimethylformamide (25 cm^3). The mixture was stirred at room temperature under argon overnight, diluted with dichloromethane (200 cm^3) and the organic fraction washed with water (100 cm^3) and an aqueous solution of hydrochloric acid (400 cm^3, 1 N). The separated aqueous layer was extracted further with dichloromethane (3 x 100 cm^3) and the combined organic fractions dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. Purification by column chromatography (SiO_2, 3% methanol in chloroform) afforded 2,3,4-trimethoxyphenoxyacetic acid as a pale brown solid (6.99 g, 28.9 mmol, 81%).

m.p. 102-104 °C; δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OMe), 3.91 (3H, s, OMe), 3.96 (3H, s, OMe), 4.66 (2H, s, CH_2), 6.59 (1H, d, *J* 9.4 Hz, H-5,), 6.67 (1H, d, *J* 9.4 Hz, H-

6); δ_C (100 MHz, $CDCl_3$) 56.7 (CH_3), 61.6 (CH_3), 62.0 (CH_3), 68.8 (CH_2), 107.1 (CH), 111.6 (CH), 143.6 (C), 144.7 (C), 145.9 (C), 150.1 (C), 173.1 (C); ν_{max} (KBr disc) 3000, 1720, 1500, 1270, 1100 cm^{-1}; *m/z* (FAB) 242 [M^+, 100%]; (Found C, 54.7; H, 5.8. $C_{11}H_{14}O_6$ requires C, 54.5; H, 5.8%).

The synthesis of compounds represented by formula (IV) will be known to those skilled in the art, but the synthesis of two compounds represented by formula (IV) is described here.

2-(3'-Hydroxy-4'-methoxyphenyl)-5,6,7-trimethoxy-4H-chromen-4-one (DR33).

The flavone **DR33** was obtained following protocol H using **DR23** (72 mg, 0.20 mmol) and potassium cyanide (130 mg, 2.00 mmol) in ethanol (3 cm^3) and dichloromethane (2 cm^3), with purification by column chromatography (SiO_2, hexane:ethyl acetate 1:5) affording **DR33** as a white solid (13 mg, 0.04 mmol, 20%).

m.p. 176-178 °C (lit. m.p. 175 °C); δ_H (400 MHz, d_6-DMSO) 3.75 (3H, s, OMe), 3.79 (3H, s, OMe), 3.85 (3H, s, OMe), 3.94 (3H, s, OMe), 6.57 (1H, s, H-3), 7.06 (1H, d, *J* 8.6 Hz, H-5'), 7.14 (1H, s, H-8), 7.42 (1H, d, *J* 2.1 Hz, H-2'), 7.49 (1H, dd, *J* 8.6 and 2.1 Hz, H-6'), 9.41 (1H, s, OH); δ_C (100 MHz, d_6-DMSO) 56.0 (CH_3), 56.7 (CH_3), 61.2 (CH_3), 62.1 (CH_3), 97.5 (CH), 106.3 (CH), 112.3 (CH), 113.0 (CH), 118.3 (CH), 123.5 (C), 140.0 (C), 147.0 (C), 150.9 (C), 151.8 (C), 154.2 (C), 157.6 (C), 160.8 (C), 175.8 (C); ν_{max} (KBr disc) 3100, 1630, 1590, 1530, 1420, 1260, 1120 cm^{-1}; *m/z* (FAB) 359 [MH^+, 100%]; (Found C, 64.0; H, 5.3. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.1%).

2-(3′-Hydroxy-4′-methoxyphenyl)-6,7,8-trimethoxy-4H-chromen-4-one (DR36).

The flavone **DR36** was obtained following protocol H using **DR27** (100 mg, 0.28 mmol) and potassium cyanide (180 mg, 2.80 mmol) in ethanol (5 cm^3), with purification by column chromatography (SiO_2, hexane:ethyl acetate 1:10) and recrystallisation from hexane:ethyl acetate affording **DR36** as a pale yellow solid (32 mg, 0.09 mmol, 32%).

m.p. 199-200 °C; δ_H (400 MHz, $CDCl_3$) 3.97 (3H, s, OMe), 3.99 (3H, s, OMe), 4.05 (3H, s, OMe), 4.10 (3H, s, OMe), 5.95 (1H, s, OH), 6.72 (1H, s, H-3), 6.98 (1H, d, *J* 8.4 Hz, H-5′), 7.40 (1H, s, H-5), 7.52 (1H, d, *J* 8.4 and 2.2 Hz, H-6′), 7.53 (1H, d, *J* 2.2 Hz, H-2′); δ_C (100 MHz, $CDCl_3$) 56.5 (CH_3), 56.7 (CH_3), 61.9 (CH_3), 62.5 (CH_3), 100.4 (CH), 106.2 (CH), 111.2 (CH), 112.7 (CH), 119.3 (CH), 120.2 (C), 125.5 (C), 142.5 (C), 146.2 (C), 146.4 (C), 147.7 (C), 149.8 (C), 151.5 (C), 163.2 (C), 178.1 (C); ν_{max} (KBr disc) 3100, 1570, 1470, 1430, 1390, 1260, 1120 cm^{-1}; *m/z* (FAB) 359 [MH^+, 50%]; (Found C, 64.0; H, 4.9. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.1%).

(E)-3-(3′′-Fluoro-4′′-methoxyphenyl)-2-methyl-1-(3′,4′,5′-trimethoxyphenyl)-2-propen-1-one (DR5).

General procedure: A solution of 3,4,5-trimethoxypropiophenone (4 mmol), substituted benzaldehyde (4 mmol), piperidine (0.8 mL) and acetic acid (0.4 ml) in ethanol (80 mL), was heated to reflux using a Soxhlet apparatus with a thimble containing activated molecular sieves to remove water from the solvent. After 4-7 days, the solvent was removed *in vacuo* and the product purified by column chromatography.

The chalcone **DR5** was obtained following protocol A using 3,4,5-trimethoxypropiophenone (0.36 g, 1.61 mmol), 3-fluoro-4-methoxybenzaldehyde (0.25 g, 1.61 mmol), piperidine (0.30 cm^3) and acetic acid (0.15 cm^3) in ethanol (3.5 cm^3). The mixture was heated at reflux under argon for 4 days. Purification by column chromatography (SiO_2, hexane:ethyl acetate 3:1) afforded **DR5** as a white solid (0.36 g, 1.00 mmol, 62%).

m.p. 84-86 °C; δ_H (300 MHz, $CDCl_3$) 2.26 (3H, s, Me), 3.89 (6H, s, OMe), 3.92 (6H, s, OMe), 6.98 (2H, s, H-2′, H-6′), 6.99 (1H, d, *J* 8.6 Hz, H-5′′), 7.08 (1H, s, H-3), 7.17 (1H, dd, *J* 8.6 and 2.0 Hz, H-6′′), 7.24 (1H, dd, *J* Hz, 13.0 and 2.0 H-2′′); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_3), 56.6 (CH_3), 56.7 (CH_3), 61.3 (CH_3), 107.5 (CH), 113.5 (CH, d, *J* 2.0 Hz), 117.6 (CH, d, *J* 15.0 Hz), 127.0 (CH, d, *J* 5.0 Hz), 129.2 (C, d, *J* 5.0 Hz), 136.1 (C), 133.8 (C), 140.3 (CH), 141.8 (C), 148.4 (C, d, *J* 15.0 Hz), 152.4 (C, d, *J* 247.0 Hz), 153.2 (C), 198.7 (C); δ_F (200 MHz, $CDCl_3$) ; ν_{max} (KBr disc) 1580, 1520, 1420, 1340, 1240, 1130 cm^{-1}; *m/z* (FAB) 361 [MH^+, 100%], 191 (80); (Found C, 66.8; H, 5.6; F, 5.6. $C_{20}H_{21}O_5F$ requires C, 66.7; H, 5.9; F, 5.3%).

3-Fluoro-4-methoxybenzaldehyde.

The method adopted was that of Diana and co-workers (Diana 1989). A stirring solution of 2-fluoroanisole (4.46 cm^3, 39.7 mmol) and hexamethylenetetramine (5.57 g, 39.7 mmol) in trifluoroacetic acid (35 cm^3) was heated at reflux under argon overnight. On cooling to room temperature the solvent was evaporated *in vacuo* and the crude residue dissolved in dichloromethane (75 cm^3). The mixture was washed with an aqueous solution of sodium

hydrogen carbonate (2 x 30 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to afford *3-fluoro-4-methoxybenzaldehyde* as a pale yellow solid (3.32 g, 21.6 mmol, 54%).

m.p. 30-31 °C (English et al., 1940 reported m.p. 29-30 °C); δ_H (300 MHz, $CDCl_3$) 3.98 (3H, s, OMe), 7.08 (1H, t, *J* 8.0 Hz, H-5), 7.60 (2H, m H-2, H-6), 9.87 (1H, d, *J* 5.0 Hz, CHO); δ_C (75 MHz, $CDCl_3$) 56.7 (CH_3), 113.1 (CH), 115.9 (CH, d, *J* 15.0 Hz), 128.6 (CH, d, *J* 3.0 Hz), 130.4 (C, *J* 5.0 Hz), 152.5 (C, d, *J* 250.0 Hz), 153.4 (C, *J* 15.0 Hz), 190.2 (CH); ν_{max} (KBr disc) 1690, 1610, 1570, 1440, 1290, 1120 cm^{-1}; *m/z* (FAB) 153 [M^+, 100%], 223 (100); (Found C, 62.3; H, 4.6. $C_8H_7O_2F$ requires C, 62.0; H, 4.5%).

(E)-3-(3'',5''-Difluoro-4''-methoxyphenyl)-2-methyl-1-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (DR6).
The chalcone **DR6** was obtained following the general method using 3,4,5-trimethoxypropiophenone (0.35 g, 1.56 mmol), 3,5-difluoro-4-methoxybenzaldehyde (0.27 g, 1.56 mmol), piperidine (0.40 cm^3) and acetic acid (0.20 cm^3) in ethanol (2.0 cm^3). The mixture was heated at reflux under argon for 4 days. Purification by column chromatography (SiO_2, hexane:ethyl acetate 3:1) afforded **DR6** as a colourless solid (0.11 g, 0.29 mmol, 19%).

δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, Me), 3.90 (6H, s, OMe), 3.95 (3H, s, OMe), 4.00 (3H, s, OMe), 6.95-7.05 (5H, m, H-3, H-2', H-6', H-2'', H-6''); δ_C (75 MHz, $CDCl_3$) 15.2 (CH_3), 56.7 (CH_3), 61.3 (CH_3), 62.2 (CH_3), 107.5 (CH), 113.8 (CH, dd, *J* 13.0 and 5.0 Hz), 130.6 (C, t, *J* 7.0 Hz), 133.2 (C), 136.9 (C, t, *J* 13.0 Hz), 138.0 (C), 138.2 (CH, split, *J* 3.0 Hz), 142.2 (C), 153.3 (C), 155.6 (C,

dd, *J* 244.0 and 7.0 Hz), 198.3 (C); δ_F (200 MHz, $CDCl_3$); ν_{max} (KBr disc) 1640, 1590, 1520, 1420, 1330, 1130 cm^{-1}; *m/z* (FAB) 379 [MH^+, 100%]; (Found C, 63.7; H, 5.2; F, 9.7. $C_{20}H_{20}O_5F_2$ requires C, 63.5; H, 5.3; F, 10.0%).

3,5-Difluoro-4-methoxybenzaldehyde.

To a stirring solution of 3,5-difluoro-4-hydroxybenzaldehyde (1.52 g, 9.6 mmol) in dimethylformamide (7.5 cm^3) was added potassium carbonate (1.99 g, 14.4 mmol) and iodomethane (0.70 cm^3, 11.5 mmol). The mixture was stirred at room temperature under argon overnight, diluted with dichloromethane (50 cm^3) and washed with an aqueous solution of sodium hydrogen carbonate (2 x 25 cm^3). The organic fraction was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to afford *3,5-difluoro-4-methoxybenzaldehyde* as a white solid (1.20 g, 7.0 mmol, 73%).

m.p. 37-38 °C (Songca 1997 reported m.p. 37-38 °C); δ_H (300 MHz, $CDCl_3$) 4.12 (3H, s, OMe), 7.43 (2H, m, H-2, H-6), 9.82 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 62.0 (CH_3), 113.9 (CH, dd, *J* 20.0 and 3.0 Hz), 130.6 (C, t, *J* 10.0 Hz), 142.2 (C, t, *J* 20.0 Hz), 157.7 (C, dd, *J* 250.0 and 10.0 Hz), 189.1 (CH); ν_{max} (KBr disc) 1700, 1620, 1590, 1520, 1450, 1390, 1340 cm^{-1}; *m/z* (EI) 172 [M^+, 100%]; (Found C, 55.7; H, 3.5; F, 21.8. $C_8H_6O_2F_2$ requires C, 55.8; H, 3.5; F, 22.1%).

Disodium 3′-phosphate salt of (E)-1-(3′-Hydroxy-4′-methoxyphenyl)-3-(3′′,4′′,5′′-trimethoxyphenyl)prop-1-en-3-one (SD174a).

According to the method of Perich and Jones (Perich 1988), 1*H*-tetrazole (408 mg, 5.82 mmol) was added in one

portion to a stirred solution of chalcone 1-(3''-hydroxy-4''-methoxyphenyl)-3-(3',4',5'-trimethoxyphenyl)-1-propen-3-one (583 mg, 1.69 mmol) and di-*tert*-butyl *N,N*-diethylphosphoramidite (0.43 cm^3, 1.54 mmol) in dry THF (5 cm^3) and stirred for 20 min at room temperature under an atmosphere of nitrogen. The mixture was then cooled down to -78 °C and a solution of *m*-CPBA (57% w/w, 631 mg, 2.08 mmol) in dry DCM (2 cm^3) was added. After stirring for 10 min at room temperature, a 10% aqueous solution of sodium bisulfite (4 cm^3) was added and the mixture stirred for a further 15 min. The aqueous mixture was then extracted with diethyl ether (50 cm^3) and the ethereal layer washed with a 10% aqueous solution of sodium bisulfite (2 × 20 cm^3), a 5% aqueous solution of sodium bicarbonate (2 × 20 cm^3), a 0.5 M aqueous solution of sodium hydroxide (2 × 20 cm^3) and finally water (20 cm^3). The ethereal layer was then dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to give the corresponding di-*tert*-butyl phosphate triether (770 mg, 1.43 mmol, 85%); *m/z* (FAB) 539 [$(M + H)^+$, 40%], 425 (30); a solution of 10 M hydrochloric acid:1,4-dioxane (1:1, 10 cm^3) was added to the residue and the reaction was allowed to stand at room temperature for 1 h. The solvent was evaporated under reduced pressure (temperature < 45 °C) and water (15 cm^3) was added to the residue. The resultant precipitate was collected and washed with chloroform (20 cm^3) to give the 3'-phosphoryl chalcone **SD173a** as a yellow oil (390 mg, 0.92 mmol, 54%). δ_H (300 MHz, d_6-DMSO) 3.07 (3H, s, OMe), 3.12 (3H, s, OMe), 3.15 (6H, s, OMe), 6.33 (1H, d, *J* 8.8 Hz, H-5'), 6.61 (2H, s, H-2'', H-6''), 6.75 (1H, dd, *J* 4.4, 8.8 Hz, H-6'), 6.88-7.00 (3H, m, H-1, H-2, H-2'); δ_P (81 MHz, d_6-

DMSO) -0.17; *m/z* (FAB) 425 [(M + H)$^+$, 100%], 424 (M$^+$, 50); chalcone **SD173a** (108 mg, 0.25 mmol) was dissolved in a 1:1 mixture of methanol:water (4 cm^3) and two drops of a 35% w/v aqueous ammonia solution were added. The mixture was applied to a Dowex 50W-X8 cation-exchange column (10 cm^3, Na$^+$), the column was eluted with a 1:1 mixture of methanol:water (30 cm^3) and the eluent was concentrated to give disodium 3′-phosphoryl chalcone **SD174a** as a bright yellow powder (87 mg, 0.19 mmol, 76%); m.p. 160 °C (dec.); ν_{max} (KBr disc) 2700-3200, 1650, 1580, 1510, 1430-1470, 1270, 1130, 990 cm^{-1}; λ_{max} (EtOH) 206.7 (log ε 4.41) and 358.9 nm (log ε 4.01); δ_H (300 MHz, d_6-DMSO) 3.07 (3H, s, OMe), 3.12 (3H, s, OMe), 3.15 (6H, s, OMe), 6.33 (1H, d, *J* 8.8 Hz, H-5′), 6.61 (2H, s, H-2′′, H-6′′), 6.75 (1H, dd, *J* 2.4, 8.8 Hz, H-6′), 6.88-7.00 (3H, m, H-1, H-2, H-2′); δ_P (81 MHz, d_6-DMSO) -87.2; [found (FAB): (M + H)$^+$, 469.0630. $C_{19}H_{20}O_9PNa_2$ requires 469.0641]; *m/z* (FAB) 491 [(M + Na)$^+$, 60%], 469 [(M + H)$^+$, 60], 329 (50), 176 (100).

Disodium 3′-phosphate salt of (E)-1-(3′-Hydroxy-4′-methoxyphenyl)-2-methyl-3-(3′′,4′′,5′′-trimethoxyphenyl)prop-1-en-3-one (SD174b).

1*H*-Tetrazole (237 mg, 3.38 mmol) was added to a stirred solution of chalcone **DR4** (970 mg, 2.71 mmol) and di-*tert*-butyl *N,N*-diethylphosphoramidite (0.75 cm^3, 2.69 mmol) in dry DCM (10 cm^3) and stirred for 20 min at room temperature under an atmosphere of nitrogen. The reaction mixture was then cooled down to -78 °C and *m*-CPBA (57% w/w, 945 mg, 3.12 mmol, dried over anhydrous magnesium sulfate) in dry DCM (5 cm^3) was added. After stirring for 10 min at room temperature, a 10% aqueous

solution of sodium bisulfite (8 cm^3) was added and the mixture was stirred for a further 15 min. The aqueous mixture was extracted with diethyl ether (30 cm^3) and the ethereal layer was washed successively with a 10% aqueous solution of sodium bisulfite (10 cm^3), a 5% aqueous solution of sodium bicarbonate (10 cm^3), a 0.5 M aqueous solution of sodium hydroxide (10 cm^3) and finally with water (10 cm^3). The solvent was removed *in vacuo* from the organic extract, the residue was redissolved in 10 M hydrochloric acid:1,4-dioxan (1:1, 10 cm^3) and then the mixture was left to stand at room temperature for 2 hours. The solvents were removed and water (20 cm^3) was added to the residue. The resultant precipitate was collected by filtration, washed with water (20 cm^3) and dissolved in a 1:1 mixture of methanol:water and 2 drops of a 35% w/v aqueous solution of ammonia were added. The mixture was applied to a Dowex 50W-X8 cation-exchange resin column (15 cm^3, Na^+), where the column was eluted with water (30 cm^3), then concentrated to give disodium 3′-phosphoryl chalcone **SD174b** as a yellow powder (40 mg, 0.083 mmol, 39%); m.p. 170 °C (dec.); ν_{max} (KBr disc) 2700-3200, 1640, 1600, 1580, 1520, 1410, 1340, 1280, 1240, 1120, 990 cm^{-1}; λ_{max} (EtOH) 208.6 (log ε 4.52) and 326.2 nm (log ε 4.12); δ_H (300 MHz, D_2O) 2.20 (3H, s, Me), 3.82 (3H, s, OMe), 3.84 (6H, s, OMe), 3.86 (3H, s, OMe), 6.98 (2H, s, H-2′′, H-6′′), 7.02 (1H, d, *J* 8.5 Hz, H-5′), 7.14 (2H, m, H-2′, H-6′), 7.60 (1H, brs, H-2); δ_C (75 MHz, D_2O) 15.2 (CH_3), 57.3 (CH_3), 57.6 (CH_3), 62.4 (CH_3), 99.9 (C), 108.8 (CH), 113.7 (CH), 123.4 (CH), 126.8 (CH), 129.6 (C), 135.9 (C), 141.4 (C), 144.4 (C), 146.7 (CH), 152.4 (C), 153.5 (C), 204.1 (C); δ_P (81 MHz, D_2O) -87.0; [found (FAB) $(M + H)^+$, 483.0812. $C_{20}H_{22}O_9PNa_2$ requires

483.0798]; *m/z* (FAB) 505 [(M + Na)$^+$, 60%], 483 [(M + H)$^+$, 75], 391 (30), 329 (30), 289 (40), 176 (100), 136 (50).

Biological Activity

The compounds of the present invention have been studied to ascertain their effectiveness as anti-cancer agents.

The compounds of the present invention have been tested for their tubulin inhibitory properties, and the results are presented in Tables 1-8, where they are compared with combretastatin A-4. The compounds of the present invention have, for convenience, been split into groups based on structural features of the compounds. The corrected values are scaled by a factor of 5 to compensate for the fact that the experimental IC50 for combretastatin A4 is lower than is often quoted in the literature.

Compound DR5 was tested for in vivo as follows. Groups of 5 nude mice were implanted s.c. in the flank with H460 human non small cell lung cells. Tumour growth was monitored by caliper measurement. Treatment was started once tumour growth had been verified. Control mice were treated with vehicle alone (arachis oil). Treatment was given daily for 5 days at 8mg/kg/day (days 17-21). Tumour volumes were calculated relative to the tumour volume on the first day of treatment (day 17 after implantation). Weight loss and general condition were monitored for the duration of the study. The experiments showed necrosis in H460 cancer cells treated with compound DR5 24 hours after treatment with 0.75 MTD. There were no adverse side effects on healthy surrounding tissue. The results of this experiment are shown in Figure 5.

Further improvement in the potency of DRA 212 was seen in an experiment in which where H460 xenograft mice were treated with X-Rays alone or were concomitantly treated with X-Rays and DRA 212 (Figure 6). Whilst X-Ray treatment was effective immediately after treatment, fresh tumour growth became evident by 36 days. In the X-Ray plus DR5 treated group, there was some initial increase in tumour volume between days 27 and 32, though this was followed by subsequent decrease to a steady baseline at day 34.

The compounds have been further tested for their performance in colchicine competition assays, and the results tabulated in Tables 9 to 13.

Table 1: Tubulin assembly inhibitory properties of 3,4,5-trimethoxyphenylchalcones.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR2	1.2	6
DR3	12	60
DR5	0.7	3.5
DR6	2.4	12
Combretastatin A-4	0.4	2.0

Table 2: Tubulin assembly inhibitory properties of water-soluble prodrugs (chalcones).

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR55	39	>100
DR56	3.1	16
combretastatin A-4	0.4	2.0

Table 3: Tubulin assembly inhibitory properties of α-methoxychalcones.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR13	0.51	2.6
DR14	0.47	2.4
DR15	1.7	8.5
combretastatin A-4	0.4	2.0

Table 4: Tubulin assembly inhibitory properties of 2,3,4-trimethoxyphenylchalcones.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR8	0.45	2.3
DR9	7.9	40
DR10	31	>100
combretastatin A-4	0.4	2.0

Table 5: Tubulin assembly inhibitory properties of aurones.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR23	>50	>100
DR24	>50	>100
DR27	22	>100
DR28	>50	>100
combretastatin A-4	0.4	2.0

Table 6: Tubulin assembly inhibitory properties of flavones.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR33	>50	>100
DR34	>50	>100
DR36	25	>100
DR37	>50	>100
combretastatin A-4	0.4	2.0

Table 7: Tubulin assembly inhibitory properties of indanones and indanols.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR57	1.9	9.5
DR58	9.8	49
DR59	4.0	20
DR60	>50	>100
combretastatin A-4	0.4	2.0

Table 8: Tubulin assembly inhibitory properties of catechol-chalcones.

Drug	IC_{50} μM (original)	IC_{50} μM (corrected)
DR31	>50	>100
combretastatin A-4	0.4	2.0

Table 9: Colchicine competition properties of chalcones.

	Drug:Protein Ratio	
Drug	10:1	1:1
DR5	6	14
DR6	25	33
combretastatin A-4	8	17

Table 10: Colchicine competition properties of water-soluble prodrugs.

	Drug:Protein Ratio	
Drug	10:1	1:1
DR55	83	100
DR56	12	100
combretastatin A-4	8	17

Table 11: Colchicine competition properties of α-alkoxychalcones.

	Drug:Protein Ratio	
Drug	10:1	1:1
DR13	5	12
DR14	8	22
DR15	41	59
combretastatin A-4	8	17

Table 12: Colchicine competition properties of aurones and flavones.

	Drug:Protein Ratio	
Drug	10:1	1:1
DR27	59	78
DR36	43	100
combretastatin A-4	8	17

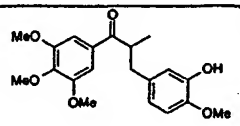
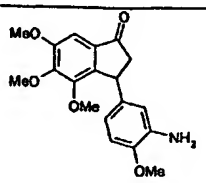
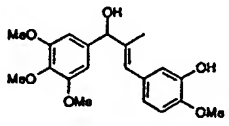
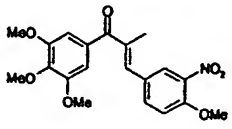
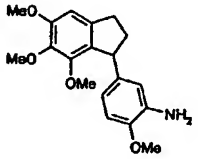
Table 13: Colchicine competition properties of indanones.

	Drug:Protein Ratio	
Drug	10:1	1:1
DR57	15	54
DR59	61	100
combretastatin A-4	8	17

Tables 14 and 15 show the results of tubulin assembly assays and flow cytometry studies on selected compounds of the present invention.

Tubulin Assembly Assay

Table 14 shows the $IC(TA)_{50}$ values calculated for selected compounds of the present invention.

Drug	Structure	$IC(TA)_{50}$	Drug	Structure	$IC(TA)_{50}$
MW71		4 μM	**MW74**		~10 μM
MW70		>10 μM	**MW68**		>10 μM
			MW82		>10 μM

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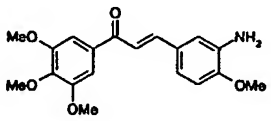
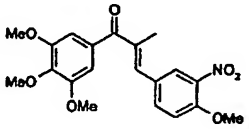
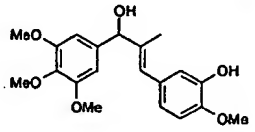
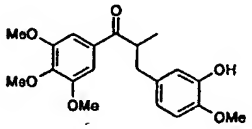
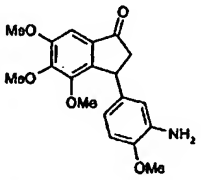
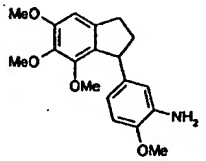
Flow Cytometry

Table 15: percentage of cells in the three phases of the cell cycle calculated by the computer program for the selected drugs.

Drug	Structure	% Cells G_0-G_1	S-phase	G_2-M	Debris
Control		55.05	32.87	12.08	
MW65		48.30	33.18	18.52	14.10
MW68		36.35	35.36	28.29	11.27
MW70		43.50	32.80	23.70	15.27
MW71		35.84	36.09	28.08	19.31
MW74		37.14	33.76	29.10	12.72
MW82		40.40	36.26	23.34	18.58

5

References

The references mentioned herein are all expressly incorporated by reference.

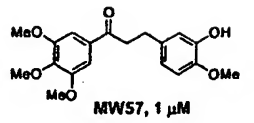
1. Arizona Board of Regents, *US 4,996,237.*
2. Ducki et al, *Bioorg. Med. Chem. Lett.*, 1998, 8, 1051.
3. Zhao et al, *Eur. J. Nuc. Medicine*, 1999, *26*, 231.
4. Aleksandrzak et al, *Anti-Cancer Drugs*, 1998, *9*, 545.
5. Lee, K.-H.; Chen, K.; Kuo, S.-C., *US 6,071,930.*
6. Edwards, M. L.; Stemerick, D. M.; Sunkara, S. P., *EP 0 288 794 A2.*
7. Clark, D.; Frankmoelle, W.; Houze, J.; Jaen, J. C.; Medina, J. C.; *WO00/35865A2.*
8. Klein, L. L. et al, *J. Med. Chem.*, 1991, 984.
9. Beutler, J. A. et al, *J. Med. Chem.*, 1998, 2333.
10. Huang, L. et al, *J. Natural Products*, 1998, 61, 446-450.
11. D. D. Pratt and R. Robinson, *J. Chem. Soc.*, 1925, 127, 173.
12. W. J. Horton and G. Thompson, *J. Am. Chem. Soc.*, 1954, 76, 1909.
13. P. K. Mahajan, Par, Yogender, Anand and Shalu, *Indian J. Chem. Sect. B.*, 1996, 35, 333.
14. D. J. Abraham, P. E. Kennedy, A. S. Mehanna, D. C. Patwa and F. L. Williams, *J. Med. Chem.*, 1984, 27, 967.
15. G. D. Diana, D. Cutcliffe, R. C. Oglesby, M. J. Otto, J. P. Mallamo, V. Akullian and M. A. McKinlay, *J. Med. Chem.*, 1989, 32, 450.
16. J. English, J. F. Mead and C. Niemann, *J. Am. Chem. Soc.*, 1940, 62, 352.
17. S. P. Songca, R. Bonnett and C. Maes, *S. Afr. J. Chem.*, 1997, 50, 40.

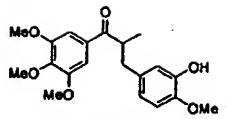
18. J. W. Perich, R. B. Johns, *Synthesis*, 1988, 142.

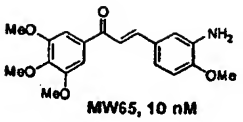
19. C. Giordano, G. Castaldi, F. Casagrande and L. Abis, *Tetrahedron Lett.*, 1982, 23, 1385.

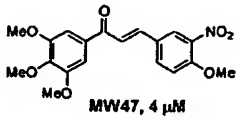
20. R. S. Varma and M. Varma, *Tetrahedron Lett.*, 1992, 33, 5937.

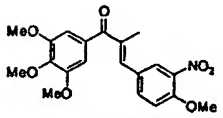
21. D. M. Fitzgerald, J. F. O'Sullivan, E. M. Philbin and T. S. Wheeler, *J. Chem. Soc.*, 195, 860.

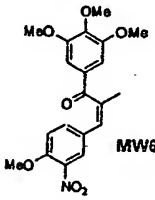

MW57, 1 μM

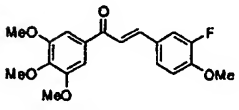

MW71, 30 nM

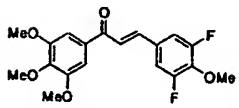

MW65, 10 nM

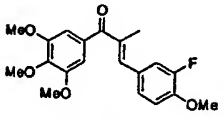

MW47, 4 μM

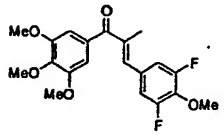

MW68, 60 nM

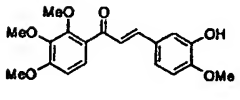

MW69, 0.2 μM

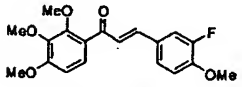

DR2, 300 nM

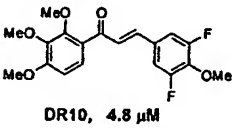

DR3, 6.2 μM

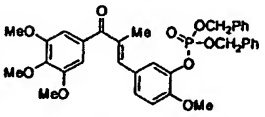

DR5, 2 nM

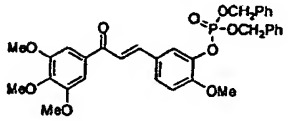

DR6, 50 nM

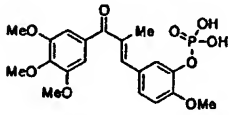

DR8, <10 nM

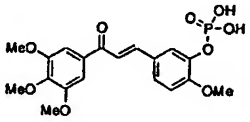

DR9, 0.35 μM

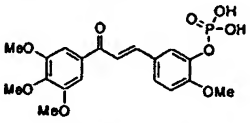

DR10, 4.8 μM

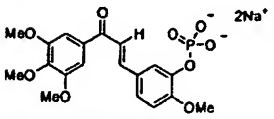

DR53, 2.8 μM

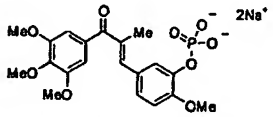

DR54, >0.05 μM

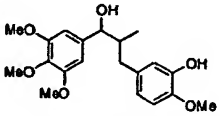

DR55, 0.33 μM

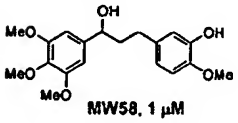

DR56, 0.5 μM

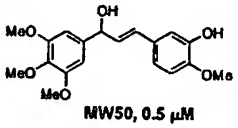

SD173a, 3.7 nM

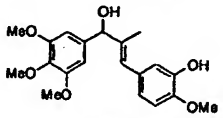

SD174a, 8 nM


SD174b, 0.12 nM


MW72, 0.6 μM


MW58, 1 μM


MW50, 0.5 μM


MW70, 90 nM

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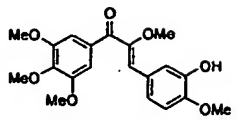
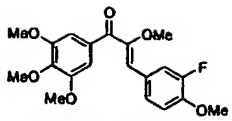
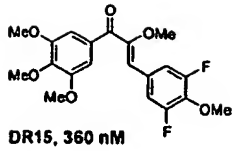
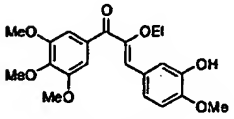
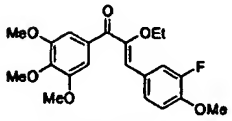
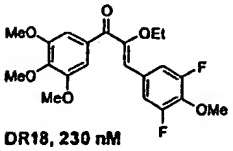

DR13, 1.6 nM

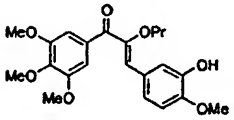

DR14, 3.7 nM

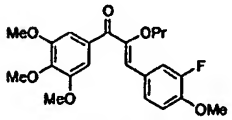

DR15, 360 nM

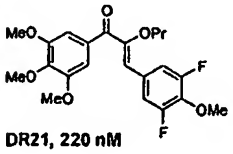

DR16, 2.6 nM

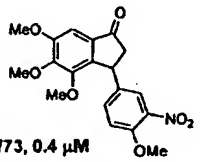

DR17, 10.5 nM

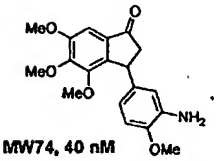

DR18, 230 nM

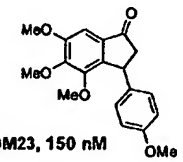

DR19

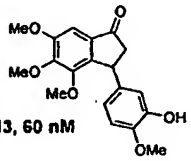

DR20, 20 nM

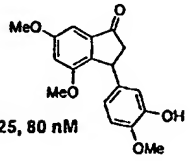

DR21, 220 nM

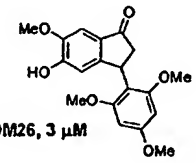

MW73, 0.4 μM

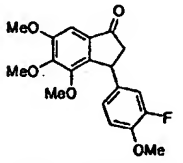

MW74, 40 nM

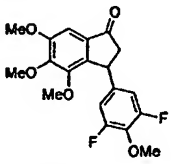

DM23, 150 nM

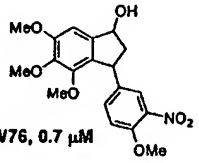

DM13, 60 nM

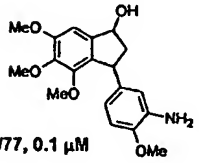

DM25, 80 nM

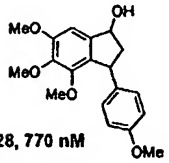

DM26, 3 μM

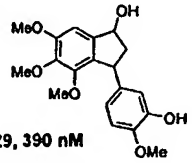

DR59, 0.12 μM

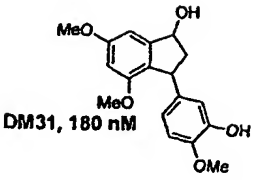

DR61, 2.1 μM


MW76, 0.7 μM

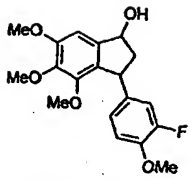

MW77, 0.1 μM


DM28, 770 nM

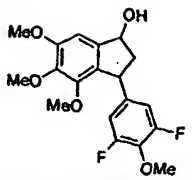

DM29, 390 nM



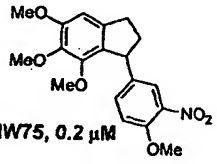
DM31, 180 nM



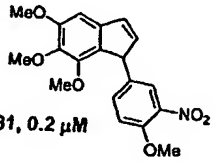
DR60, 5.7 μM



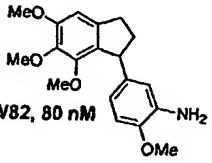
DR62, >50 μM



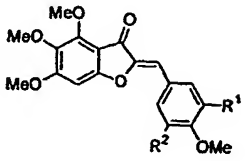
MW75, 0.2 μM



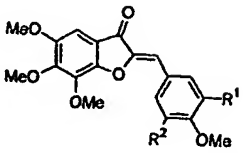
MW81, 0.2 μM



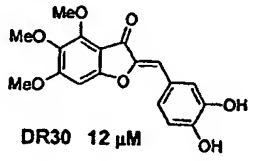
MW82, 80 nM



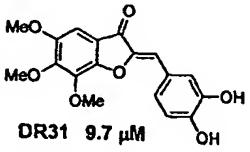
DR22 (R^1 = H, R^2 = H) >50 μM
DR23 (R^1 = OH, R^2 = H) 18 μM
DR24 (R^1 = F, R^2 = H) >50 μM
DR25 (R^1 = F, R^2 = F) >50 μM



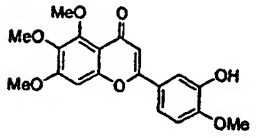
DR26 (R^1 = H, R^2 = H) 0.15 μM
DR27 (R^1 = OH, R^2 = H) 50 nM
DR28 (R^1 = F, R^2 = H) 110 nM
DR29 (R^1 = F, R^2 = F) 9.7 μM



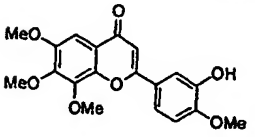
DR30 12 μM



DR31 9.7 μM



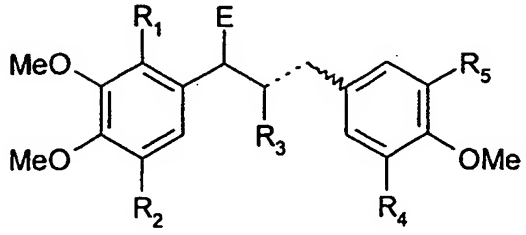
DR33, 22 nM



DR36, 40 nM

Claims:

1. A compound represented by formula I:

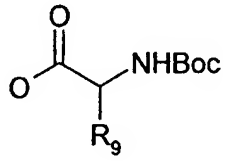


(I)

wherein:

E represents an oxo (=O) or a hydroxyl (-OH);
the dashed line indicates that a single or double bond may be present;
the zig-zag line indicates that the compound can be either the E or Z isomer;

R_3 is H, alkyl, CH_2NH_2, $CH_2NHalkyl$, CH_2OH, $CH_2N(alkyl)_2$, $CH_2NH(C=O)alkyl$, $CH_2NH(C=O)aryl$; and
R_4 is H, halogen, NH(alkyl), $N(alkyl)_2$, $NH(C=O)alkyl$, $NH(C=O)aryl$, or a Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain;
and further wherein:

when E is an oxo (=O) group and the dashed line represents a single bond,
R_1 is H; R_2 is alkoxy; R_4 is H; and R_5 is OH; or

when E is an oxo (=O) group and the dashed line represents a double bond,
R_1 is H; R_2 is alkoxy; R_4 is H or halogen; and
R_5 is H or halogen; or

R_4 is H; and R_5 is NH_2, NO_2, halogen or $OPO_3(R_6)_2$; where R_6 is H, CH_2Ph or a metal cation; or
R_1 is alkoxy; R_2 is H; R_4 is H or halogen; and
R_5 is halogen or OH; or

when E is a hydroxyl (-OH) group and the dashed line represents a single or double bond,
R_1 is H; R_2 is alkoxy; R_3 is methyl; R_4 is H; and R_5 is OH;

or a salt or derivative thereof.

2. The compound of claim 1, wherein the compound is a compound represented by formula I where:

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is OH (MW57);

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is OH (MW71);

E is an oxo (=O) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is NH_2 (MW65);

E is an oxo (=O) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is NO_2 (MW47);

E is an oxo (=O) group; the dashed line represents a double bond; the compound is the E isomer; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is NO_2 (MW68);

E is an oxo (=O) group; the dashed line represents a double bond; the compound is the Z isomer; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is NO_2 (MW69);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is F (DR2);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is F; and R_5 is F (DR3);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is F (DR5);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is F; and R_5 is F (DR6);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is OMe; R_2 is H; R_3 is H; R_4 is H; and R_5 is OH (DR8);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is OMe; R_2 is H; R_3 is H; R_4 is H; and R_5 is F (DR9);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is OMe; R_2 is H; R_3 is H; R_4 is F; and R_5 is F (DR10);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5

is $OPO_3(R_6)_2$ wherein R_6 is CH_2Ph (DR53);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is CH_2Ph (DR54);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is H (DR55);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is H (DR56);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is H (SD173a);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is Na (SD174a);

E is an oxo (=O) group; the dashed line represent a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is $OPO_3(R_6)_2$ wherein R_6 is Na (SD174b);

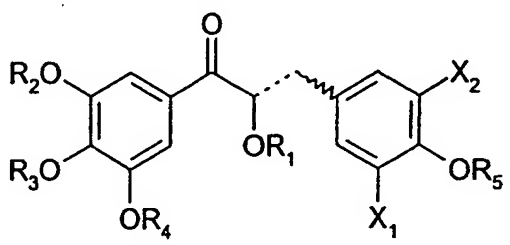
E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is OH (MW72);

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is OH (MW58);

E is a hydroxyl (-OH) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; and R_5 is OH (MW50);

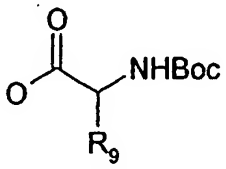
E is a hydroxyl (-OH) group; the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is Me; R_4 is H; and R_5 is OH (MW70).

3. A compound represented by formula Ia:



wherein:
the dashed line indicates that a single or double bond may be present;
the zig-zag line indicates that the compound can be either the E or Z isomer;

R_1 is alkyl; R_2, R_3, R_4 and R_5 are independently selected from H or alkyl; X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', $O\text{-}P{=}O(OR)_2$, O-aryl, O-heteroaryl, O-ester or a Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain;

or a salt or derivative thereof.

4. The compound of claim 3, wherein the compound is a compound represented by formula Ia where:

the dashed line represent a double bond; R_1 is Me; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is OH (DR13); or

the dashed line represent a double bond; R_1 is Me; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is F (DR14); or

the dashed line represent a double bond; R_1 is Me; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 and X_2 are F (DR15); or

the dashed line represent a double bond; R_1 is Et; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is OH (DR16); or

the dashed line represent a double bond; R_1 is Et; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is F (DR17); or

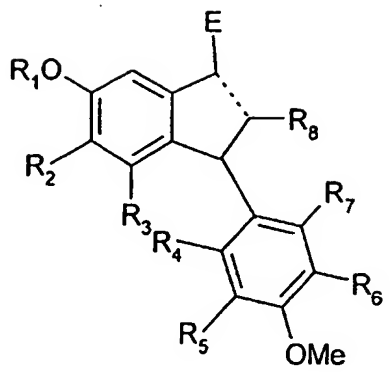
the dashed line represent a double bond; R_1 is Et; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 and X_2 are F (DR18); or

the dashed line represent a double bond; R_1 is Pr; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is OH (DR19); or

the dashed line represent a double bond; R_1 is Pr; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is H; and X_2 is F (DR20); or

the dashed line represent a double bond; R_1 is Pr; R_2, R_3 and R_4 are Me; R_5 is Me; X_1 is F; and X_2 is F (DR21).

5. A compound represented by formula II:



(II)

wherein:

E represents an oxo (=O), hydroxyl (-OH) or a hydrogen atom;

the dashed line in the structure indicates that a single or double bond may be present; and

R_8 is hydrogen, alkyl, aryl, CH_2NH_2, CH_2NHalkyl or $CH_2N(alkyl)_2$; and wherein:

when E is an oxo (=O) group and the dashed line represents a single bond,

R_1 is alkyl or H; R_2 is alkoxy or H; R_3 is alkoxy or H; and R_4 is H; R_5 is H, $O(P=O)(OR)_2$ or Boc-ester; R_6 is NO_2, NH_2, H, OH, halogen, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H; or

R_4 is H; R_5 is halogen, $O(P=O)(OR)_2$ or Boc-ester; R_6 is OH, halogen, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H; or

R_4 is alkoxy; R_5 is H, $O(P=O)(OR)_2$ or Boc-ester; R_6 is H, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is alkoxy; or

when E is a hydroxyl (-OH) group and the dashed line represents a single bond,

R_1 is alkyl; R_2 is H or alkoxy; R_3 is alkoxy; R_4 is H; R_5 is alkoxy, halogen, $O(P=O)(OR)_2$ or Boc-ester;

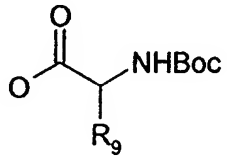
R_6 is H, NO_2, NH_2, OH, halogen, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H; or

when E is a hydrogen atom and the dashed line represents a double bond,

R_1 is Me; R_2 is alkoxy; R_3 is alkoxy; R_4 is H; R_5 is H, $O(P=O)(OR)_2$ or Boc-ester;

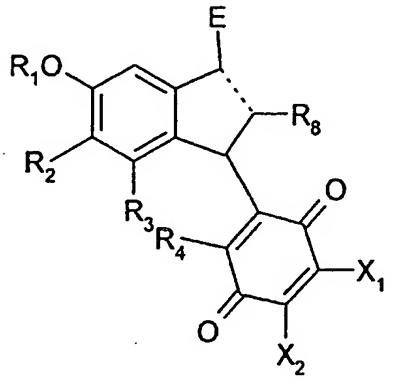
R_6 is NO_2, NH_2, NHMe, $NHMe_2$, NH(C=O)alkyl or NH(C=O)aryl; and R_7 is H;

wherein the Boc-ester is a group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain; or

a compound represented by structural formula IIa:



(IIa)

wherein:

E, R_1, R_2, R_7 and R_8 are as defined above; and

X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-aryl, O-heteroaryl or O-ester; or

or a salt or derivative of compounds II or IIa.

6. The compound of claim 4, wherein when the compound is a compound represented by formula II where:

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; R_7 is H (MW73); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NH_2; and R_7 is H (MW74); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is H; and R_7 is H (DM23); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM13); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is H; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM25); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OH; R_3 is H; R_4 is OMe; R_5 is H; R_6 is H; and R_7 is OMe (DM26); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is F; and R_7 is H (DR59); or

E is an oxo (=O) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is F; R_6 is F; and R_7 is H (DR61); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; R_7 is H (MW76); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NH_2; and R_7 is H (MW77); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is H; and R_7 is H (DM28); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM29); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is H; R_3 is OMe; R_4 is H; R_5 is H; R_6 is OH; and R_7 is H (DM31); or

E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is F; and R_7 is H (DR60); or

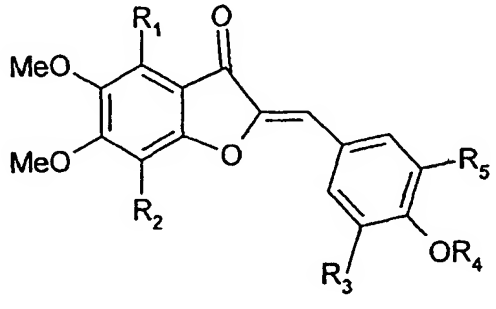
E is a hydroxyl (-OH) group; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is F; R_6 is F; and R_7 is H (DR62); or

E is a hydrogen atom; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; and R_7 is H (MW75); or

E is a hydrogen atom; the dashed line represents a double bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NO_2; and R_7 is H (MW81); or

E is a hydrogen atom; the dashed line represents a single bond; R_1 is Me; R_2 is OMe; R_3 is OMe; R_4 is H; R_5 is H; R_6 is NH_2; and R_7 is H (MW82);

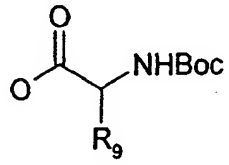
7. A compound represented by formula III:



(III)

wherein:

R_1 is H or alkoxy; R_2 is H or alkoxy; R_3 is H or halogen; R_4 is H or alkyl; and R_5 is H, OH, halogen, $O(P=O)(OR)_2$ or a Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain;

or a salt or derivative thereof.

8. The compound of claim 7, wherein the compound is a compound represented by formula III where:

R_1 is OMe; R_2 is H; R_3 is H; R_4 is Me; R_5 is H (DR22); or

R_1 is OMe; R_2 is H; R_3 is H; R_4 is Me; R_5 is OH (DR23); or

R_1 is OMe; R_2 is H; R_3 is H; R_4 is Me; R_5 is F (DR24); or

R_1 is OMe; R_2 is H; R_3 is F; R_4 is Me; R_5 is F (DR25); or

R_1 is H; R_2 is OMe; R_3 is H; R_4 is Me; R_5 is H (DR26); or

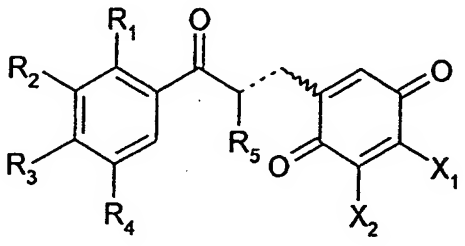
R_1 is H; R_2 is OMe; R_3 is H; R_4 is Me; R_5 is OH (DR27); or

R_1 is H; R_2 is OMe; R_3 is H; R_4 is Me; R_5 is F (DR28); or

R_1 is H; R_2 is OMe; R_3 is F; R_4 is Me; R_5 is F (DR29); or

R_1 is H; R_2 is OMe; R_3 is H; R_4 is H; R_5 is OH (DR31).

9. A compound represented by formula IV:



(IV)

wherein:

the dashed line indicates that a single or double bond may be present;

the zig-zag line indicates that the compound can be either the E or Z isomer; and

R_1, R_2, R_3 and R_4 are independently selected from H or alkoxy;

R_5 is hydrogen, alkyl, alkoxy or O-aryl; and

X_1 and X_2 are independently selected from H, OH, nitro, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-aryl, O-heteroaryl or O-ester;

or a salt or derivative thereof.

10. The compound of claim 9, wherein the compound is a compound represented by formula IV where the dashed line represents a double bond; R_1 is H; R_2 is OMe; R_3 is OMe; R_4 is OMe, X_1 is OMe, and X_2 is H.

11. The compound of any one of the preceding claims, wherein said alkyl substituent is a substituted or unsubstituted methyl or ethyl group.

12. The compound of any one of the preceding claims, wherein said alkoxy substituent is a substituted or unsubstituted methoxy, ethoxy or propoxy group.

13. The compound of any one of the preceding claims, wherein said halogen group is a fluorine group.

14. The compound of any one of the preceding claims, wherein the salt or derivative is a salt, an ester, a free acid or base, a hydrate, a prodrug or the compound linked to a coupling partner.

15. The compound of claim 14, wherein the salt is a sodium phosphate salt, a sodium salt, a potassium salt, a

lithium salt, a magnesium salt, a calcium salt, a manganese salt, a zinc salt, a salt with an ammonium cation selected from imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline and verapamil.

16. The compound of claim 14, wherein the ester is a Boc-ester, a hemisuccinic acid ester, a phosphate ester, a sulphate ester or a selenate ester.

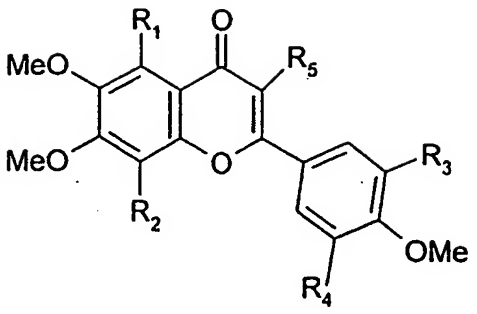
17. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a salt or derivative thereof, and a carrier.

18. A compound of any one of claims 1 to 16 for use in a method of medical treatment.

19. Use of a compound of any one of claims 1 to 16 for the preparation of a medicament for the treatment of cancer or a condition involving abnormal proliferation of vasculature.

20. The use of claim 19, wherein the condition is diabetic retinopathy, psoriasis or endometriosis.

21. A compound represented by structural formula V for use in a method of medical treatment:



(V)

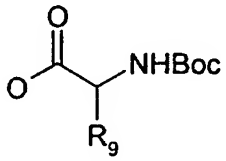
wherein:

R_1 or R_2 is alkoxy and the other is H;

R_3 and R_4 are different and are hydrogen, halogen, OH, $O(P=O)(OR)_2$ or Boc-ester;

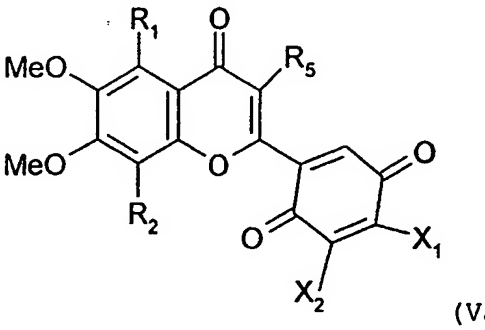
R_5 is aryl, alkyl or O-alkyl;

wherein the Boc-ester group represented by:



wherein R_9 is alkyl, CH_2Ph where Ph is a substituted or substituted phenyl group, or an amino acid side chain; or

a compound of represented by structural formula Va in which:



(Va)

wherein:

R_1, R_2 and R_5 are defined as above;

X_1 and X_2 are independently selected from H, OH, nitro,

amino, aryl, heteroaryl, alkyl, alkoxy, CHO, COR, halogen, haloalkyl, NH_2, NHR, NRR', SR, $CONH_2$, CONHR, CONHRR', O-aryl, O-heteroaryl or O-ester; or

or a salt or derivative of compounds V or Va.

22. The compound of claim 21, wherein the compound is a compound represented by formula V where:

R_1 is OMe; R_2 is H; R_3 is OH; and R_4 is H; or

R_1 is OMe; R_2 is H; R_3 is F; and R_4 is H; or

R_1 is H; R_2 is OMe; R_3 is OH; and R_4 is H; or

R_1 is OMe; R_2 is H; R_3 is F; and R_4 is H.

23. Use of a compound of claim 21 or claim 22 for the preparation of a medicament for the treatment of cancer or a condition involving abnormal proliferation of vasculature.

24. The use of claim 23, wherein the condition is diabetic retinopathy, psoriasis or endometriosis.

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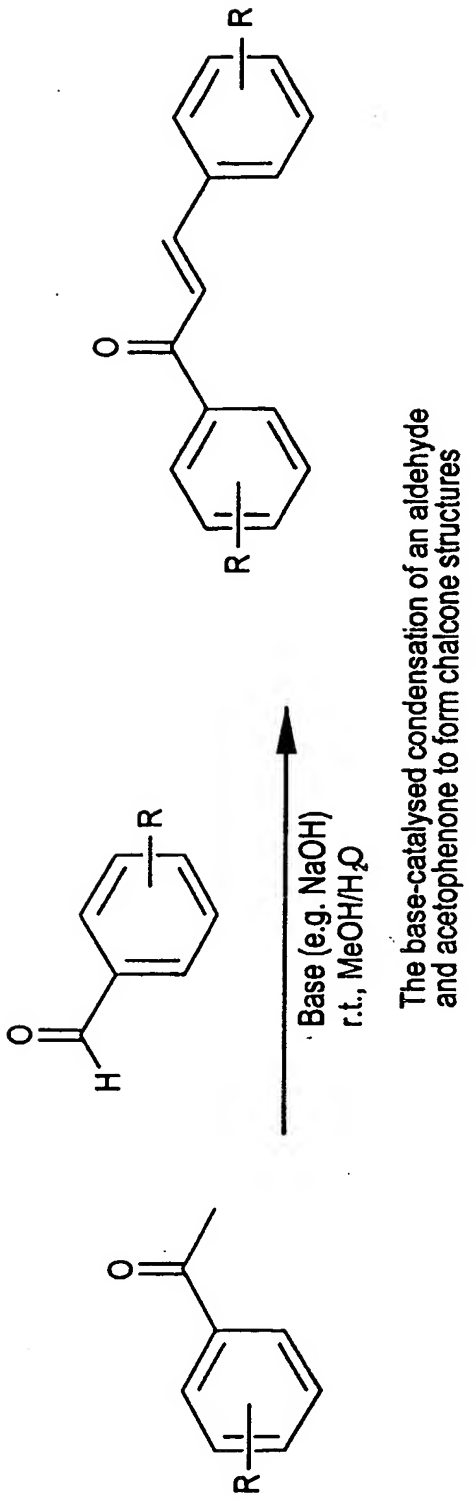
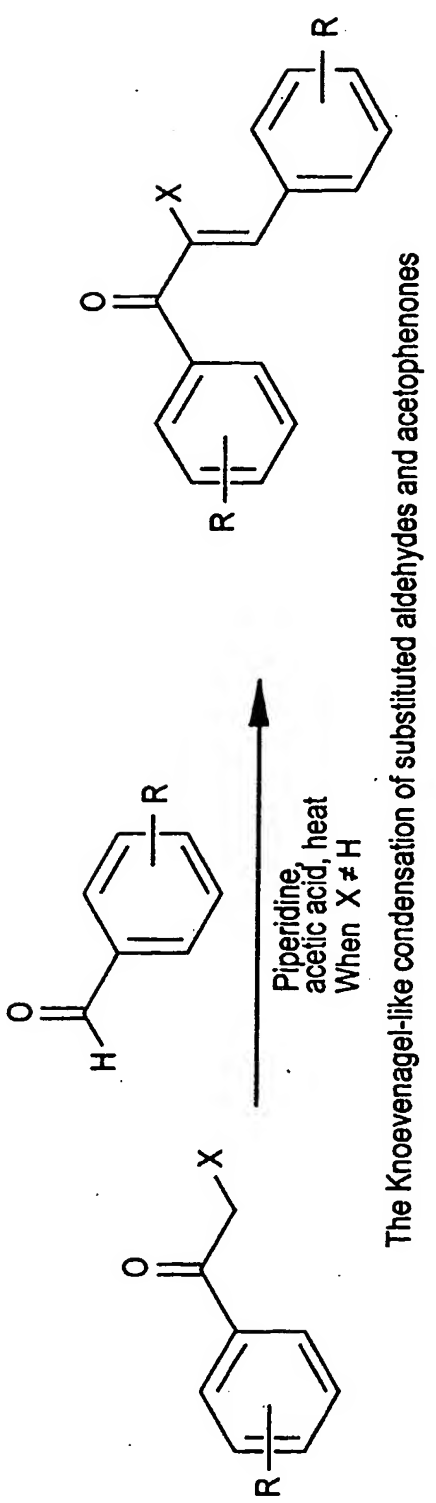


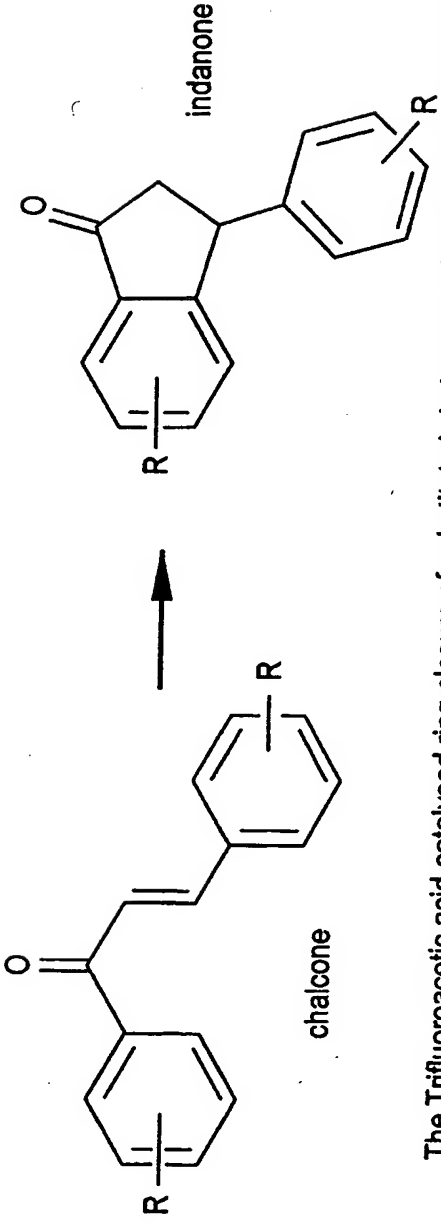
The base-catalysed condensation of an aldehyde and acetophenone to form chalcone structures

Fig. 1



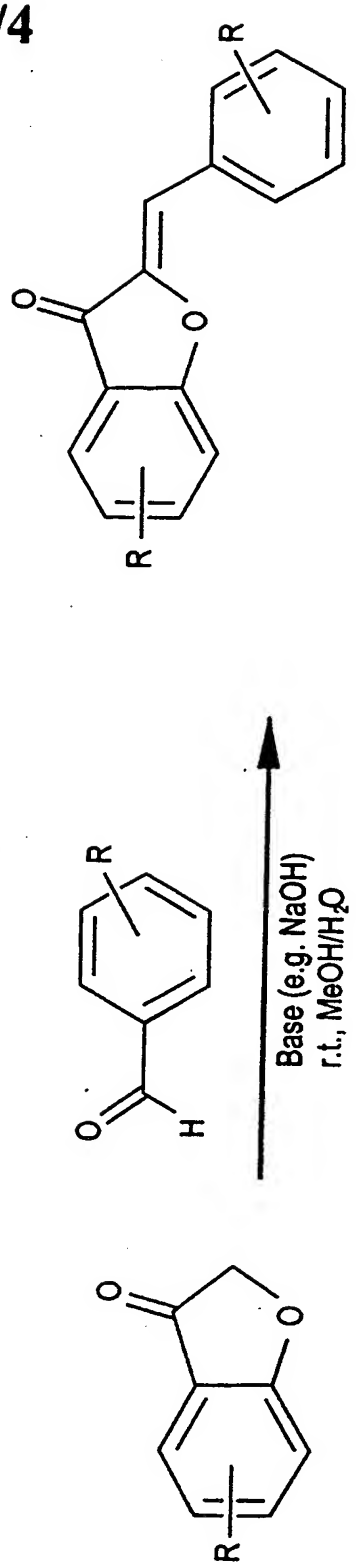
The Knoevenagel-like condensation of substituted aldehydes and acetophenones

Fig. 2



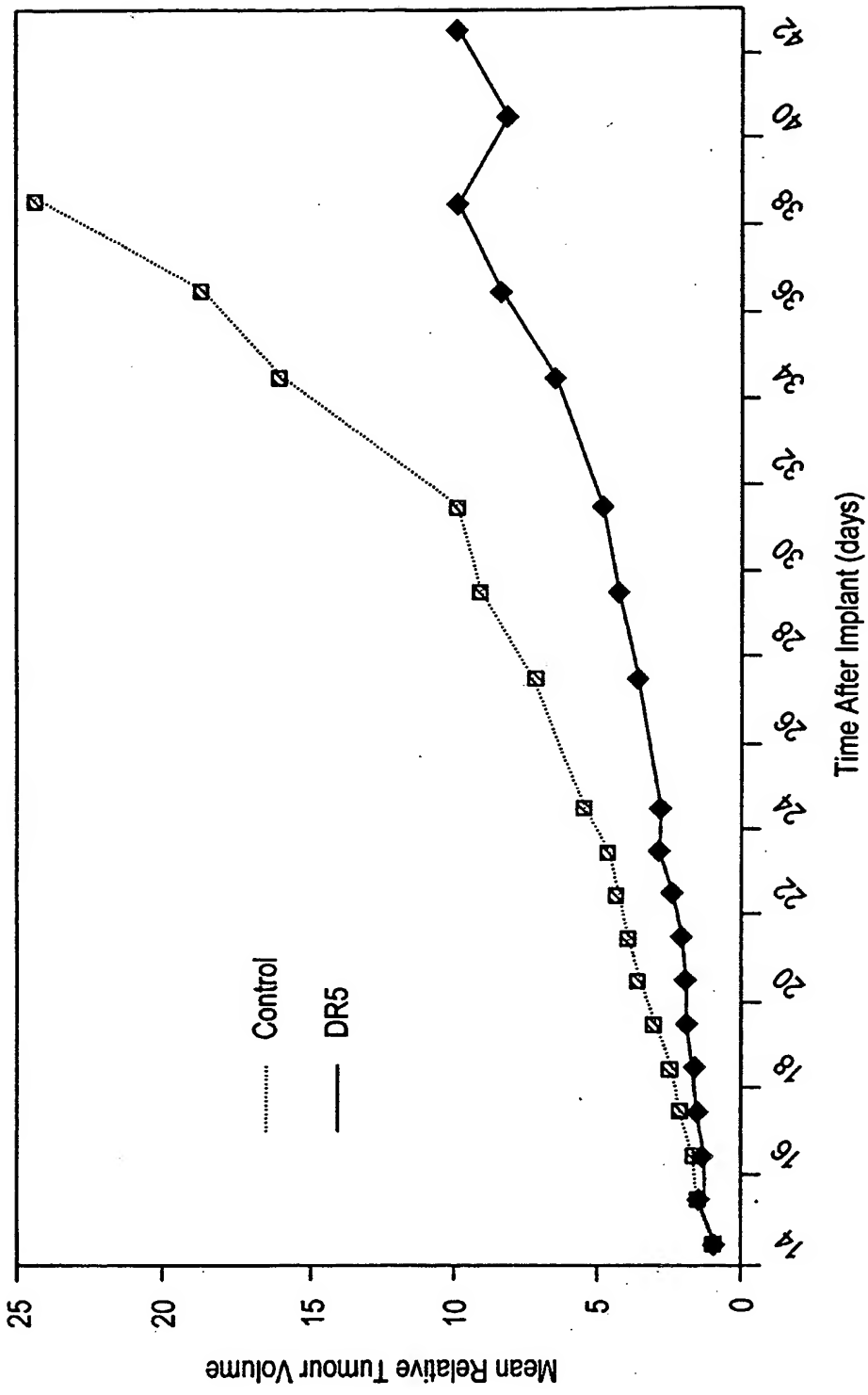
The Trifluoroacetic acid-catalysed ring-closure of substituted chalcones to form substituted indanones

Fig. 3



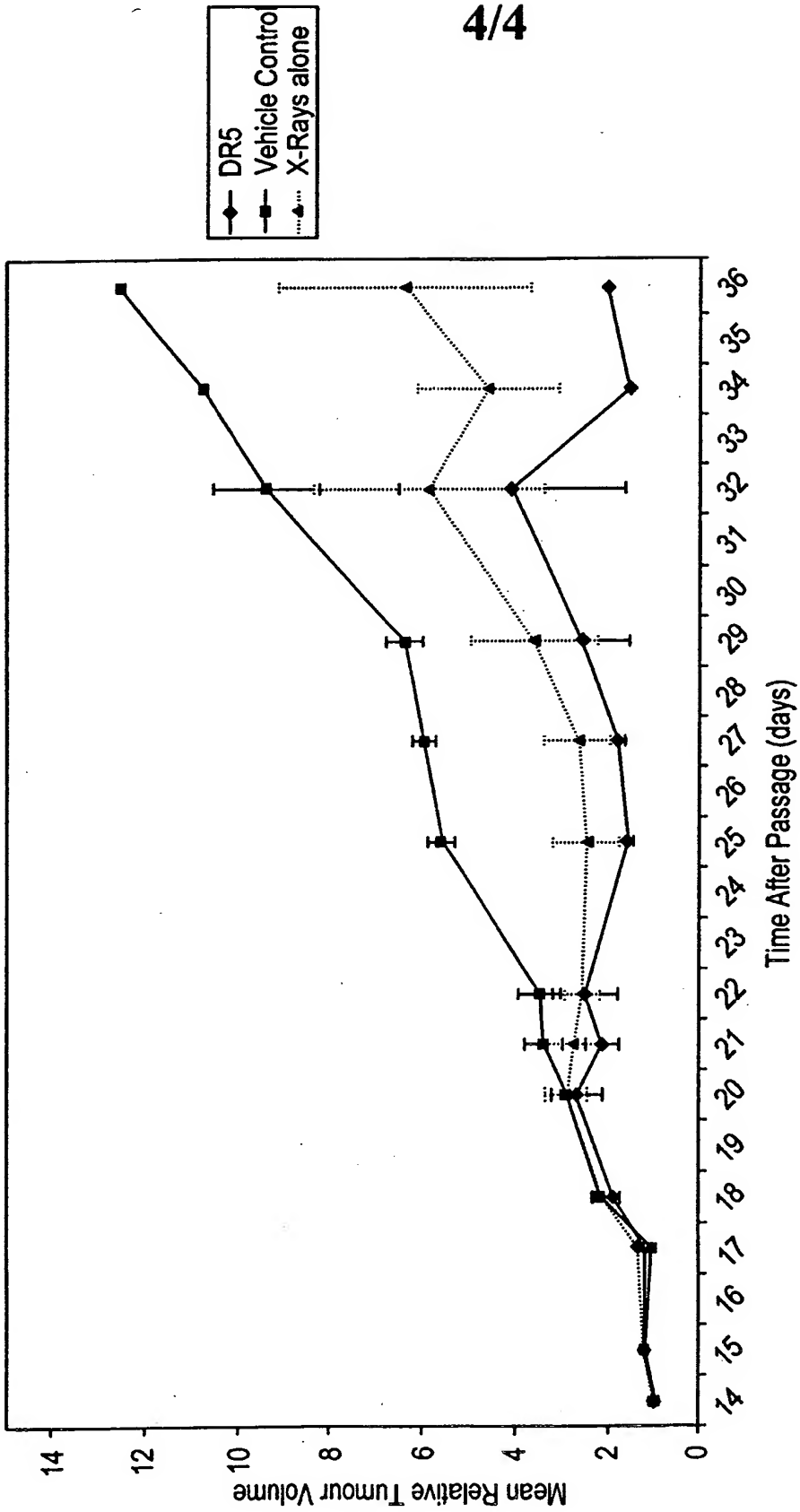
The base-catalysed formation of aurones from substituted aldehydes and benzofuranones

Fig. 4



Anti-Tumour Activity of DR5 (40mg/kg/day on days 17-21 inc.)

Fig. 5



Anti-Tumour Activity of DR5 (40mg/kg/day on days 18-22 inc.)

Fig. 6

INTERNATIONAL SEARCH REPORT

PCT/GB 02/05055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C49/83 C07C49/755 C07C211/46 C07C43/295 A61K31/12
A61K31/36 A61K31/09 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 40056 A (BURKE MICHAEL DANNY ;BUTLER PAUL CRISPIN (GB); PATTERSON LAWRENCE) 12 August 1999 (1999-08-12) see compound VII claims 7-14	1,12, 17-19
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 4474127 XP002231765 abstract & TETRAHEDRON LETT, vol. 24, no. 28, 1983, pages 2851-2854,	5

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2003	06/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2591569 XP002231766 abstract & ACTA CHIM ACAD SCI HUNG, vol. 40, 1964, pages 295-305,	5
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 1300680 XP002231767 abstract & CHEM BER, vol. 97, 1964, page 2857	21
A	EP 0 288 794 A (MERRELL DOW PHARMA) 2 November 1988 (1988-11-02) cited in the application the whole document	1
A	WO 00 35865 A (TULARIK INC) 22 June 2000 (2000-06-22) cited in the application claim 15	21

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INTERNATIONAL SEARCH REPORT

PCT/GB 02/05055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9940056 A	12-08-1999	AU 2173899 A	23-08-1999
		CA 2319836 A1	12-08-1999
		EP 1051383 A1	15-11-2000
		WO 9940056 A1	12-08-1999
		JP 2002502836 T	29-01-2002
		US 6214886 B1	10-04-2001
		US 2001021717 A1	13-09-2001
EP 0288794 A	02-11-1988	US 4904697 A	27-02-1990
		AT 106723 T	15-06-1994
		AU 599220 B2	12-07-1990
		AU 1416488 A	13-10-1988
		DE 3889970 D1	14-07-1994
		DE 3889970 T2	06-10-1994
		DK 192188 A	10-10-1988
		EP 0288794 A2	02-11-1988
		JP 2603099 B2	23-04-1997
		JP 63267749 A	04-11-1988
		PH 25183 A	27-03-1991
		ZA 8802391 A	23-09-1988
WO 0035865 A	22-06-2000	AU 2190700 A	03-07-2000
		WO 0035865 A2	22-06-2000
		US 6433187 B1	13-08-2002